

**RESPONSE TO RADIOIODINE THERAPY IN MALE HYPERTHYROID PATIENTS
AT TYGERBERG HOSPITAL
ONIMODE, YETUNDE AJOKE**

Thesis presented in partial fulfilment of the requirements for the degree of Master of
Science (Nuclear Medicine) at the Stellenbosch University

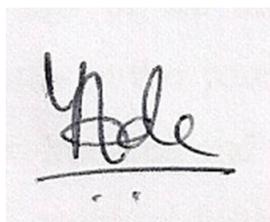


Supervisors: Prof Annare Ellmann
Dr Nisaar Korowlay

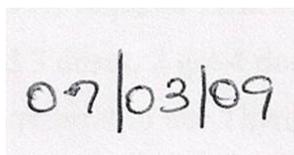
March 2009
All rights reserved

Author's declaration

By submitting this thesis electronically, I declare that the entirety of the work contained therein is my own original work, that I am the owner of the copyright thereof (unless to the extent explicitly otherwise stated) and that I have not previously in its entirety or in part submitted it for obtaining any qualification.

A handwritten signature in black ink on a light-colored background. The signature appears to be 'Y. de' with a horizontal line underneath.

Signature

A handwritten date in black ink on a light-colored background, written as '07/03/09'.

Date

Abstract

Radioiodine therapy is reputed to yield poorer results in male patients than in females. We retrospectively reviewed the records of 308 patients treated with radioiodine-131 (RAI) for Graves' disease (n=266, 86.4%), toxic multinodular goitres (n=35, 11.4%) and toxic solitary nodules (n=7, 2.3%).

The mean age of the men was 44 ± 13.6 years (range 14-77 years). Patients with GD were predominantly in the younger age groups, while those with toxic nodular goitres were in the older range. Two hundred and fifty-nine patients (84.1%) were treated with a single dose of RAI, while 49 (15.9%) required further doses. A second dose had to be administered to 38 patients, while 8 received 3 doses, 2 got 4 doses and 1 patient had 5 doses in all (these included a first dose received prior to referral to our Thyroid Clinic). Cure was determined as euthyroidism or hypothyroidism at the 3-month follow-up visit.

The average pre-treatment T4 value was 68.9 ± 31.8 pmol/L (range 5.7 – 155 pmol/L); while the mean Tc-99m pertechnetate uptake value was $15.8 \pm 10.9\%$ (range 0.88 - 62.9).

Patients with GD presented with more severe hyperthyroidism than the other patients; mean free T4 of 71.9 ± 31.1 pmol/L compared to 51.4 ± 29.9 pmol/L for the TMG group of patients, and 39.6 ± 26.8 pmol/L for the TSN group (ANOVA $p < 0.0001$, confirmed by the Kruskal-Wallis test). Patients with TMG and TSN were treated with higher doses than patients with GD; mean first doses of 349.3 ± 88.5 MBq and 428.1 ± 28.6 MBq respectively, compared to a mean dose of 325.1 ± 69.3 MBq for patients with GD. Treatment with multiple doses of RAI correlated with higher values of T4 and T3 at presentation ($p < 0.0001$). However, none of the baseline variables of age, T4 and T3, and first dose of RAI was significant predictors of free T4 outcome at 3 months. A consistently higher dose was administered to the male patients, compared to female patients of similar age, diagnosis and level of thyrotoxicosis (Tc-99m pertechnetate uptake). Despite this, male patients had similar outcomes as the female patients 3 months after therapy.

Our findings lend weight to the theory that male patients are more difficult to treat than their female counterparts, seeing that the former had similar outcomes despite the significantly higher doses of RAI administered to the males.

Opsomming

Radiojodium terapie lewer na bewering swakker resultate in mans as in vroulike pasiënte. Die inligting van 308 pasiënte met Grave se siekte ($n=266$, 86.4%), toksiese multinodulêre tiroïed ($n=35$, 11.4%) en enkel toksiese nodules ($n=7$, 2.3%) wat met radiojodium ($I-131$) behandel is, is retrospektief nagegaan.

Die gemiddelde ouderdom van die mans was 44 ± 13.6 jaar (reikwydte 14-77 jaar). Die meeste pasiënte met Grave se siekte was in die jonger ouderdomsgroep, terwyl dié met toksiese multinodulêre tiroïed, ouer was. Tweehonderd nege-en-vyftig pasiënte (84.1%) is met 'n enkel dosis radiojodium behandel, terwyl 49 (15.9%) meer as een dosis benodig het. 'n Tweede dosis is aan 38 pasiënte gegee, terwyl agt 3 dosisse, twee 4 dosisse en 1 pasiënt 5 dosisse in totaal ontvang het (wat 'n eerste dosis voor verwysing na die tiroïedklinik, ingesluit het). Herstel is gedefinieer as eutiroidisme of hipotiroidisme tydens die drie maande opvolgbesoek.

Die gemiddelde T4-waarde voor behandeling was 68.9 ± 31.8 pmol/L (reikwydte 5.7–155 pmol/L); terwyl die gemiddelde Tc-99m pertegnetaatopname $15.8 \pm 10.9\%$ (reikwydte 0.88–62.9) was.

Pasiënte met Grave se siekte het met erger hipertiroïdisme as die ander pasiënte gepresenteer; met 'n gemiddelde vry T4 van 71.9 ± 31.1 pmol/L vergeleke met 51.4 ± 29.9 pmol/L vir die toksiese multinodulêre tiroïedgroep en 39.6 ± 26.8 pmol/L vir die enkel toksiese nodule groep (ANOVA $p<0.0001$, bevestig met die Kruskal-Wallis-toets). Pasiënte met toksiese multinodulêre tiroïed en enkel toksiese nodule, is met hoër dosisse as dié met Grave se siekte behandel; met 'n gemiddelde eerste dosis van 349.3 ± 88.5 MBq en 428.1 ± 28.6 MBq onderskeidelik, vergeleke met 'n gemiddelde dosis van 325.1 ± 69.3 MBq vir pasiënte met Grave se siekte. Behandeling met meer as een dosis radiojodium het gekorreleer met hoër T4- en T3- waardes by ($p<0.0001$). Geen van die basislyn veranderlikes (ouderdom, T4 en T3, en die eerste dosis radiojodium) was egter 'n betekenisvolle voorspeller van die vry T4 uitkoms op 3 maande nie. Die dosis wat aan manlike pasiënte toegedien is, was konstant hoër, vergeleke met die vroulike pasiënte van dieselfde ouderdom, diagnose en vlak van tirotoksikose. (Tc-99m pertegnetaatopname). Ongeag hiervan, was die uitkoms by manlike en vroulike pasiënte 3 maande na terapie dieselfde.

Ons bevindinge dra by tot die teorie dat manlike pasiënte moeiliker is om te behandel as hul vroulike eweknieë, aangesien mans soortgelyke uitkomste gehad het ten spyte van betekenisvol hoër dosisse radiojodium.

Dedication

This thesis is dedicated to God Almighty, Who made and inspires me, to Prof & Mrs Onimode, strict educators who instilled in me a love for learning, and also to Segun, Kayode and Jumoke Onimode who supported me all the way.

Acknowledgements

I would like to thank the following people and organizations who have contributed, in their own way, to making this thesis a reality: Mrs A Onimode and the Onimode family, Prof BOA Osifo, Prof A Ellmann, Prof SM Rubow, Prof DG Nel, Dr C Meyer, Mr Kleinhans and the staff of the Tygerberg Hospital Chemical Pathology Department, Dr N Lambwe, Pastor and Pastor (Mrs) Oduwole, Dr A Assasie-Gyimah, Mrs I De Klerk, Mrs E Beetge, Ms C Fluks and the staff of the Department of Nuclear Medicine, University College Hospital, Ibadan, Oyo State, Nigeria. Support for this thesis was provided by the International Atomic Energy Agency, Vienna, Austria.

Table of contents

Declaration	i
Abstract	ii
Opsomming	iii
Dedication	iv
Acknowledgements	v
CHAPTER 1	
Introduction	1
CHAPTER 2	
Physiology and pathophysiology of the thyroid	3
CHAPTER 3	
Evaluation of the hyperthyroid patient	11
CHAPTER 4	
Treatment of hyperthyroidism	19
CHAPTER 5	
Materials and methods	28
CHAPTER 6	
Results	31
CHAPTER 7	
Discussion and conclusion	41
References	46

CHAPTER 1
INTRODUCTION

Thyroid dysfunction can occur from overproduction or underproduction of thyroid hormones by the thyroid gland. It may be secondary to disease of the thyroid gland itself (primary hyperthyroidism/hypothyroidism), or from disease of the pituitary and hypothalamus (secondary hyperthyroidism/hypothyroidism). Autoimmune disease of the thyroid gland as well as competitive drug reactions can all culminate in thyroid dysfunction.

Although the two terms are often used interchangeably, hyperthyroidism is distinct from thyrotoxicosis in that the latter is characterized by hypermetabolism due to increased circulating thyroid hormone, while hyperthyroidism is thyrotoxicosis from a hyperfunctioning thyroid gland.^{1,2,3,4} It occurs mainly in females but is also seen in men; its prevalence has been quoted as 2% of all women and 0.2% of men^{5,6}, or to be five to twelve times more likely to occur in females than in males.^{7,8} In both genders, the main age of presentation is in the reproductive years. Over 99% of cases are caused by intrinsic thyroid disease.⁸

Hyperthyroid patients are an important group of patients in Nuclear Medicine thyroid practice, as they comprise the majority of referrals.⁹ Hyperthyroidism is fraught with significant morbidity from the unpleasant signs and symptoms that accompany it, such as thyrotoxic heart failure. Primary hyperthyroidism can be treated by medical or surgical means, or with the use of radioactive iodine-131 (RAI). The decision as to which modality to utilize differs from country to country and also depends on patient preference.^{10,11} The majority of physicians in Belgium, the United Kingdom, and the United States would rather treat hyperthyroid patients with RAI, while those in Denmark, The Netherlands, Germany and Switzerland prefer antithyroid medication as first-line therapy. The choices these physicians made were not affected by patient gender, or the presence or absence of goitre. Most physicians opted for RAI if the patient was being treated for recurrent hyperthyroidism, and almost all chose to give younger patients antithyroid medication rather than surgery or RAI.

Treatment of primary hyperthyroidism using I-131 has been in use for over 30 years. It is relatively cheap, easy to administer, avoids patient default of treatment because it is administered by the managing nuclear physician, is in the majority of cases administered once, and has few sequelae (except hypothyroidism which can be corrected using thyroid supplements).⁴

The dose of RAI to administer to each patient depends on factors such as the age, gender, and the severity of hyperthyroidism (determined by free thyroid hormones, radioiodine and/or Tc-99m pertechnetate uptake).

However, there exists a paucity of literature on the effect of gender on patient outcome, specifically the male patients, in whom the disease is less common.

The effect of gender on treatment outcome has been examined by Allahabadia and co-workers who found a significant association between patient age at diagnosis and gender, and failure of medical treatment and RAI.^{12,13} Other factors have been described as affecting the efficacy of RAI; such as

pretreatment with antithyroid medication, size of goitre, smoking and the administered dose.^{14,15,16,17}

In an earlier study of 241 male patients with Graves' disease undertaken by Bland and Hays, racial status has also been demonstrated as a factor influencing outcome of RAI therapy¹⁸

Our study investigates the manner in which male hyperthyroid patients react differently compared to their female counterparts, after having been treated with empirical dose(s) of radioactive iodine-131.

CHAPTER 2
PHYSIOLOGY AND PATHOPHYSIOLOGY OF THE THYROID

Physiology of the thyroid gland

Normal iodine metabolism^{19,20}

The normal daily minimum intake of iodine required to maintain normal thyroid function is 150 µg; the average amount of iodine ingested daily is 500 µg. Ingested iodine is converted to iodide (I⁻) in the gut and then absorbed. The normal plasma iodide level is 0.3 µg/dL. The principal organs of iodine uptake are the thyroid gland and the kidneys; the latter are its excretory organs. This is important when calculating dosimetry during radioactive iodine treatment.

Approximately 120 µg/day of iodide enters the thyroid gland at normal rates of thyroid hormone synthesis and secretion, of which 80 µg is secreted as iodine in thyroid hormones. The remaining 40 µg diffuses back into extracellular fluid.

Secreted thyroid hormone is metabolized in the liver and other tissues, releasing 60 µg of iodide into extracellular fluid (ECF). Some hormone derivatives are secreted into bile and into the enterohepatic circulation; others, containing 20 µg of iodide, are lost in stool. Inorganic iodide undergoes rapid clearance by the kidneys such that approximately 485 µg is excreted in urine. The ECF iodide pool therefore contains approximately 150 µg of iodide. As such, the total amount of iodide that enters the extracellular fluid compartment is 600 µg, of which 20% enters the thyroid while 80% is excreted in urine.

The intrathyroidal iodine pool²¹

The intrathyroidal iodine pool is in equilibrium with plasma iodine at a gradient of as high as 50:1 to 100:1 (intrathyroidal : plasma iodine) in the euthyroid state. This ratio may increase up to 400:1 during treatment with antithyroid drugs, and up to 500:1 *in vitro* in mice when organification was inhibited.^{22, 23}

Tyrosine-bound iodine no longer contributes to the equilibrium gradient. This allows more iodine to be trapped to maintain the gradient.²⁴

Thyroid hormone synthesis

1. Uptake

Dietary iodine is reduced to iodide in the gut.²² Thyroid follicular cells concentrate iodide from the blood by a basally located iodide pump, the sodium-iodide symporter (NIS), whose activity is stimulated by the thyroid stimulating hormone (TSH) and inhibited by monovalent anions like perchlorate, pertechnetate, thiocyanate, nitrate, and excess iodide. Pertechnetate, perchlorate and thiocyanate have a stronger affinity for the NIS than does iodide.²⁵ The ability of the thyroid to accumulate iodide via the NIS has been the basis for diagnostic scintigraphy of the thyroid and for

radioactive iodine therapy of hyperfunctioning thyroid tissue, and thyroid carcinoma. Perchlorate blockade of iodine uptake has also been applied clinically, for example, to protect the thyroid gland from unwanted irradiation when administering radioiodine-based tracers.^{25, 26} The salivary glands, gastric mucosa, choroid plexus, ciliary body of the eye, and the mammary glands also exhibit iodide uptake but TSH does not regulate these other sites.¹⁹

2. Oxidation

Iodide is oxidized to iodine by peroxidase and transported to the plasma membrane, where it is released into the lumen of the follicle.

3. Thyroglobulin synthesis

The synthesis of thyroglobulin occurs in the rough endoplasmic reticulum. The product is packaged by the Golgi apparatus and released into the lumen of the follicle by exocytosis.

4. Organification

Thyroglobulin, iodide, peroxidase (and hydrogen peroxide) are essential for organification to occur. In the lumen of the follicle, iodine and tyrosine residues of thyroglobulin combine (iodination) to form moniodotyrosine (MIT) and diiodotyrosine (DIT), catalyzed by peroxidase. These in turn undergo coupling (also catalyzed by peroxidase) to form the hormones triiodothyronine (T_3) and thyroxine (T_4). T_3 is formed by the coupling of a molecule of MIT and another of DIT, while T_4 is formed by the combination of two molecules of DIT. The hormones remain bound to thyroglobulin in their inactive forms. This step can be blocked by antithyroid drugs, and also following radiation and inflammation. Such a block would lead to reduced formation of thyroid hormone.

Excess iodide can cause a mild and transient inhibition of this step on account of increased concentration of iodide in the thyroid (the Wolff-Chaikov effect)¹⁹ A biphasic response has been described in which there is initially an increase, and later, a decrease in the amount of iodide being organified.²⁵ The Wolff-Chaikov effect is more likely to occur when there is stimulation of iodine trapping, and when iodide transport is increased (as occurs in thyrotoxic patients hence they are more responsive to iodide than normal individuals are). Patients with organification defects are also said to be more prone to the effect, for example, patients on antithyroid drug therapy, and those whose thyroid glands have previously been irradiated. Long-standing exposure to excess iodide can produce goitre and hypothyroidism.

Excess iodide also inhibits proteolysis, and lessens the response of cyclic AMP to TSH.

5. Storage

The iodinated thyroglobulin molecule comprises most of the colloid.¹⁹ Colloid is the storage form for both thyroid hormone and iodine. A third of the iodine found in thyroglobulin is in form of thyroid hormones, while the rest is in the form of inactive hormone precursors.

6. Proteolysis of thyroglobulin

This requires re-entry of the thyroglobulin-hormone complex into the thyroid cell. The thyroglobulin-hormone complex is engulfed by pinocytosis into cytoplasmic vacuoles. The vacuoles are acted on by lysosomes that contain hydrolases. These enzymes cleave the hormones and iodinated precursors (iodotyrosines) from thyroglobulin. Iodotyrosines are deiodinated by an iodotyrosine-specific deiodinase present in thyroid tissue and their released iodide becomes an important source of iodine for hormone synthesis. Excess iodide also inhibits this step.

7. Release

Thyroid hormones are released at the base of the cell and diffuse into the bloodstream. Both thyroglobulin proteolysis and thyroid hormone release are blocked by antithyroid drugs.

Sites of action

Synthesis and exocytosis occur at the apex of the cell. Thyroglobulin endocytosis from colloid, breakdown of the thyroglobulin-hormone complex and the release of free hormone occur at the base of the cell.

Regulation of thyroid hormone synthesis^{19,24,27,28,29}

TSH is the most important regulator of thyroid homeostasis. Its production is controlled by the stimulatory effect of the hypothalamic thyrotropin-releasing hormone (TRH) based on a negative feedback loop from circulating free T₃ and T₄.

Functions of thyroid hormones^{8,19}

Triiodothyronine is the more metabolically active hormone, and is more potent than thyroxine.^{19,22}

Thyroid hormones cause the following effects:

1. Calorigenic effects

There is increased oxygen consumption by all metabolically active tissues except the adult brain, testes/uterus, lymph nodes, spleen, and the anterior pituitary. The increase in metabolic rate that occurs following one dose of T₄ lasts 6 days or more. With this increase in metabolic rate, the excretion of nitrogen is increased. Therefore, stores of protein and fat in the body are catabolized, leading to weight loss if food intake is not adequately increased.

Large doses of thyroid hormone may cause the production of excess heat such that mechanisms of heat dissipation set in; cutaneous vasodilatation and decrease peripheral resistance occur, but cardiac output, blood pressure, tachycardia and circulation time increase owing to the effect of thyroid hormone and catecholamines.

2. Nervous system

Thyroid hormones help with brain development, especially of the cerebral cortex, basal ganglia and cochlea. Large doses cause rapid mentation, irritability and restlessness. Reflexes have a shorter reaction time in hyperthyroidism. Maturation of the CNS *in utero* requires the presence of thyroid hormone, such that hypothyroidism causes mental retardation.

3. Cardiac effects

These are produced primarily by the action of T_3 on cardiac myocytes. Indirect effects are produced by catecholamines, the sympathetic nervous system, haemodynamic changes and by increased cardiac output from an increase in metabolic rate. An increase in the number and affinity of β -adrenergic receptors in the heart is seen, resulting in an increased sensitivity to the inotropic and chronotropic effects of catecholamines. There is increased production of α -MHC myosin (heavy chain myosin isoform), which increases the speed of cardiac contraction.

4. Catecholamine-associated effects

Adrenaline released by the sympathetic nervous system in response to thyroid hormone secretion, causes an increased metabolic rate, and stimulates the nervous and cardiovascular systems. Noradrenaline produces similar symptoms.

5. Skeletal system/ Growth

Thyroid hormones are necessary for normal growth and skeletal maturation; they are required for the attainment of adult stature. They stimulate bone turnover, increasing both osteogenesis and bone resorption. Deficiency of thyroid hormones causes delayed closure of epiphyses. They potentiate the effect of growth hormone on tissues.

6. Skeletal muscle

Hyperthyroid myopathy may be partly due to the increased protein catabolism that occurs with elevated thyroid hormone levels.

7. Endocrine effects

Thyroid hormones act together with growth hormone and somatomedins to promote bone formation.

8. Gastrointestinal effects/ carbohydrate metabolism

Increased absorption of carbohydrate from the gut occurs in the thyrotoxic state; glycosuria may occur in thyrotoxicosis when postprandial plasma glucose levels exceed the renal threshold. Increased appetite and diarrhoea are also known to occur in thyrotoxic states.

10. Cholesterol metabolism

Thyroid hormones lower blood cholesterol levels independent of their calorogenic action, by increasing the number of LDL receptors in the liver and by increasing the hepatic removal of cholesterol from the circulation.

Pathophysiology of the thyroid gland

Thyroid dysfunction can occur from overproduction or underproduction of thyroid hormone, which may occur from disease of the thyroid gland itself (primary hyperthyroidism/hypothyroidism), or from disease of the pituitary and hypothalamus (secondary hyperthyroidism/hypothyroidism). Autoimmune disease and infection of the thyroid gland, competitive drug reactions, can all culminate in thyroid dysfunction.

Hyperthyroidism

In the context of this thesis, the relevant conditions are primary hyperthyroidism from Graves' disease, toxic multinodular goitres and toxic solitary nodules. The following events occur in hyperthyroidism:¹⁹

1. Increased levels of circulating thyroid hormone are found.
2. T₃ exerts a negative feedback effect on the anterior pituitary and on the hypothalamus.
3. Decreased secretion of TRH and TSH occur.
4. When thyroid hormone levels normalize, TSH is released from its repressed state and returns to normal. This does not occur instantaneously but rather over months.

Causes of hyperthyroidism

The discussion of the aetiology of hyperthyroidism will focus on the three main causes of primary hyperthyroidism, namely Graves' disease, toxic multinodular goitre, and toxic solitary nodule.

1. Graves' disease

It is an autoimmune disease and the commonest cause of hyperthyroidism.^{8,30} There are thyroid-stimulating immunoglobulins (80% positive), thyroid growth-stimulating immunoglobulins, and TSH-binding immunoglobulins (60-90% positive),⁸ which all act to produce the hyperthyroid state. Triggers for Graves' disease have been described; environmental factors such as stress, infection, pregnancy, food and sex steroids.³¹ Infection (for example, with *Yersinia enterocolitica*, *Escherichia coli*)^{8,32,33,34} has also been associated with autoimmune thyroid disease. The mechanisms of these triggers may involve molecular mimicry and T-cell autoimmunity. A 50% concordance rate has been described in monozygote twins. The natural history fluctuates between relapse and remission. Pathologic features show the following:

- The thyroid is mildly and symmetrically enlarged, with an intact capsule.
- There is widespread hypertrophy and hyperplasia of follicular epithelium.
- Colloid is decreased substantially.
- There is hyperplasia of lymphoid tissue and increased vascularity of the gland.
- In patients with Graves' ophthalmopathy, orbital tissues are oedematous because of hydrophilic mucopolysaccharides.
- Lymphocyte infiltration and fibrosis occur in advanced stages.

2. Toxic multinodular goitre

This is irregular thyroid enlargement caused by recurrent episodes of stimulation and involution of a diffuse goitre. It is commoner in older women.^{1,2} The multinodular goitre is frequently mistaken for a neoplasm. Pathologic features are as follows:

- The gland is multilobulated and asymmetrically enlarged. The goitre may be large enough to produce pressure symptoms on the trachea and oesophagus.
- A plunging or intrathoracic goitre may develop if it grows behind the sternum and clavicles.
- Focal haemorrhage, fibrosis, calcification and cystic change are responsible for the nodularity of the gland.
- Its histology is variable; colloid accumulation, epithelial hyperplasia and follicular involution may be seen.

3. Toxic solitary nodule

It is responsible for about 5% of hyperthyroid cases;⁸ most solitary thyroid nodules are non-functioning. It occurs in 5% of patients with a solitary palpable nodule, and is more frequently seen in the elderly and in people living in areas of iodine deficiency. Autonomous nodules are reputed to cause thyrotoxic symptoms when they reach a size of 2.5 – 3 cm.²

Clinical features of hyperthyroidism⁸

Changes seen in hyperthyroid patients are referable to the hypermetabolic state that is created and to the overactivity of the sympathetic nervous system.

Symptoms include the following: weight loss (children may gain weight), increased appetite, irritability, tremor, heat intolerance mainly, as well as palpitations, goitre, excessive sweating, diarrhoea, eye complaints, restlessness, malaise, stiffness, muscle weakness, breathlessness, itching, thirst, vomiting, diarrhoea, oligomenorrhoea, onycholysis, loss of libido, gynaecomastia, tall stature (in children), and choreoathetosis.

Major signs are: tremor, hyperkinesis, tachycardia or atrial fibrillation, full/bounding pulse, warm vasodilated peripheries, lid lag and 'stare', goitre, bruit, exophthalmos (only in Graves' disease).

Others are weight loss, irritability, conjunctival oedema, periorbital oedema, systolic hypertension, cardiac failure (high output), ophthalmoplegia (only in Graves' disease), proximal myopathy, proximal muscle wasting, onycholysis, palmar erythema, Graves' dermopathy, thyroid acropachy (the latter two only in Graves'), pretibial myxoedema, and psychosis.

CHAPTER 3
EVALUATION OF THE HYPERTHYROID PATIENT

There are various modalities available for the investigation of thyrotoxicosis. Diagnosis of thyrotoxicosis is made biochemically with thyroid function tests. The aetiology of the patient's thyrotoxic status can then be confirmed as Graves' disease, toxic multinodular goitre, or solitary toxic nodule. This will help in clinical decision-making and in the choice of management modality for the patient. Investigations of value to confirm the abovementioned conditions include the thyroid scintigram and thyroid radioiodine/ ^{99m}Tc -pertechnetate uptake, thyroid ultrasonography, and fine needle aspiration cytology. CT, MRI and ^{18}F -FDG scans have little or no role in the routine imaging of the hyperthyroid patient and will therefore not be discussed in detail. Other tests like antibody assays are mostly available in specialist centres and are also not routinely carried out. As was done in the previous chapter, discussion of the evaluation of hyperthyroid patients will be limited to Graves' disease, the toxic multinodular goitre and the toxic solitary nodule.

The thyroid scintigram

The thyroid scintigram is radionuclide imaging of the thyroid gland. Thyroid scanning in patients with thyrotoxicosis is necessary for the following reasons:³⁵

- To assess thyrotoxic goitre and thus confirm thyrotoxicosis as being primary in origin
- To differentiate among cases of Graves' disease, toxic multinodular goitre and toxic solitary nodule
- To determine the functional status of thyroid nodules in a patient with a toxic multinodular goitre or solitary toxic nodule
- To exclude suspected thyroiditis³⁶

Thyroid scans are done using ^{99m}Tc -pertechnetate or ^{123}I or ^{131}I . ^{99m}Tc -pertechnetate, from a Mo-99/Tc-99m generator, behaves similarly to iodide based on its similar ionic characteristics. It undergoes uptake into the thyroid gland.³⁷ Uptake by the thyroid requires cellular integrity and cellular energy. ^{99m}Tc -pertechnetate does not undergo organification; therefore it cannot be used to evaluate suspected enzyme deficiencies, or hormone resistance.^{36,38,39} Maximal thyroid uptake of ^{99m}Tc -pertechnetate occurs about 20 minutes post-administration; it plateaus at 20-30 minutes and decreases thereafter.² ^{99m}Tc -pertechnetate is favoured for imaging because of its short physical half-life of six hours, low-energy gamma emissions of 140keV and reduced radiation dose to the patient when compared to the radioiodines.

^{123}I sodium iodide is a cyclotron product, supplied as a capsule or solution of sodium iodide. ^{131}I sodium iodide is produced in the nuclear reactor from uranium fission, or from neutron activation of tellurium. For the purposes of RAIU, ^{123}I is preferred for its smaller radiation dose, which is one-tenth that from ^{131}I .³⁸ Sodium iodide is absorbed through the intestine and reaches its peak blood

level after 3 hours. The 24-hour delay in imaging after administration of the dose is not on account of poor gland uptake but rather for improved background clearance.² As a thyroid hormone precursor, radioiodine is trapped by the thyroid and concentrated in a ratio 6:1 compared to its plasma level. It is organified and subsequently bound to thyroglobulin.

Assessment of gland size, shape and location are made. The distribution of the radiopharmaceutical is noted. A comparison of uptake of tracer by the thyroid to that of salivary glands and to background activity can also be noted. The presence of nodules, whether of greater or less intensity than surrounding thyroid tissue, is also noted. Information that is helpful in the interpretation of the thyroid scan includes relevant laboratory data (including thyroid function tests) and the results of previous thyroid imaging. The merits and demerits of using radioactive iodine or ^{99m}Tc-pertechnetate as tracers in thyroid imaging are outlined in Table 3.1.

Scintigraphic findings

Graves' disease typically is seen as diffuse and increased uptake of tracer in an enlarged thyroid. The toxic multinodular goitre has inhomogeneous uptake, with more intense uptake in the toxic nodules. The solitary toxic nodule has increased tracer uptake with partial or complete suppression of the rest of the gland. Retrosternal extension of the gland can also be noted.

Table 3.1: Comparison of radiopharmaceuticals for thyroid scintigraphy^{35,40,41}

Property	^{99m} TcO ₄ ⁻	¹²³ I-sodium iodide	¹³¹ I-sodium iodide
Imaging qualities	Ideal for gamma camera	Similar to those of ^{99m} Tc	Not ideal for imaging
Cost and availability	Cheap and readily available	Most expensive Not readily available	Fairly cheap and readily available
Radiation dose to target organ (mGy/MBq)	Least radiation dose; 0.062 (upper large bowel) ¹	Less radiation dose than with ¹³¹ I; 1.9 (thyroid) ²	Highest radiation dose of all three; 210 (thyroid) ³
Advantages	Earlier imaging.	Better results of nodule imaging than with ^{99m} Tc-pertechnetate True measure of thyroid function	Better results of nodule imaging than with ^{99m} Tc-pertechnetate. True measure of thyroid function Later imaging
Disadvantages	Trapped but not organified Poor image quality when uptake is low	Most expensive of the three	High radiation dose to patient from β-radiation. High-energy gamma radiation causes poorer imaging than with ¹²³ I. Later imaging time

TcO₄⁻= Tc-99m pertechnetate

¹ICRP 53, p.199, no blocking agent

²ICRP 53, p. 264, assuming 15% uptake

³ICRP 53, p.276, assuming 15% uptake

Table 3.2: Scintigraphic patterns in the hyperthyroid patient^{2,42}

Disease	Thyroid scan pattern	%Pertechnetate uptake
Graves' disease	Diffuse increased uptake	Virtually always elevated
Toxic multinodular goitre	Inhomogeneous uptake in toxic adenomas with suppression of rest of gland	High normal to moderately increased
Solitary toxic nodule	Increased uptake in nodule with complete or partial suppression of rest of gland	High normal to increased

Thyroid uptake tests

The percentage uptake of radiopharmaceutical by the thyroid gland is a measure of its trapping ability. If scintigraphy is performed along with the uptake measurement, both visual and quantitative assessments of uptake can be made, comparing thyroid tissue uptake to salivary gland and background activity. Otherwise, uptake measurements can be made using the thyroid probe.

International guidelines describe the use of Tc-99m pertechnetate and ¹²³I sodium iodide for thyroid uptake measurement.^{10,35} The thyroid does not organify ^{99m}Tc-pertechnetate, but in the majority of cases uptake (and imaging) data provide the information needed for accurate diagnosis.⁴¹

1. Radioiodine uptake

Iodine-131 was the first radioisotope used for uptake and imaging studies of the thyroid gland.¹¹ Its main role is in the evaluation of thyrotoxicosis to distinguish thyroiditis from goitre, to show the feasibility of radioiodine therapy, and to aid in calculation of the dose.^{42,43} Radioiodine can also be used in the investigation of organification defects.⁴¹

RAIU is usually determined at 24 hours after administration of I-123 or I-131, to allow for incorporation of radioiodine into the thyroid gland. Berg and co-workers⁴⁴ advocate measurement at different times after the administration of the RAI, for example, up to 6 days. They made use of effective half-life measurements of ¹³¹I for up to 6 days post-administration of therapy on the premise that these would indicate the period of retention of tracer dose and assist with the calculation of the therapeutic radioiodine dose. Two methods of RAIU for dose calculation were compared; the first using the effective half-life of ¹³¹I at 24 and 48 hours, and at 4 or 6 days, and the other using a fixed effective half-life measurement of 5 days. The second method resulted in under- and overtreatment of Graves' disease, and in overtreatment of toxic multinodular goitre. Patients with Graves' disease were found to have significantly shorter effective half-life measurements of ¹³¹I than those patients with toxic multinodular goitres. Likewise, patients who had been treated

with antithyroid medication before RAIU had a shorter effective half-life measurements than those who were not pre-treated. The implication of this was that a short effective half-life could result in under-treatment if not taken into consideration during dose calculation. Hooper et al⁴² concur that a lower value of RAIU requires that larger doses of RAI be given and advise that RAIU be used to calculate the dose to be administered.

Earlier assessment of uptake has been advocated, based on the concept that some hyperthyroid patients might have peak uptakes in the first few hours after administration of the tracer, with progressive falls in uptake levels so that the 24-hour values may not be the peak value, as is seen in Graves' disease. A 5 hour/24 hour ratio >1 means that there is rapid turnover of iodine, and a short effective half-life of radioiodine, with the implication as discussed above.^{42,45,46}

Hennessy et al in a study of 22 men and 77 women advocated early I-123 uptake calculations to estimate the dose of I-131 for therapy of hyperthyroidism, rather than the 24-hour I-123 uptake calculation, based on the highly significant correlation between doses calculated using predicted uptake values (from the early I-123 uptake results) and actual measured I-123 uptake results at 24 hours.⁴⁷

Initial preparation for the uptake measurement involves stopping antithyroid drug therapy 3-4 days beforehand, as well as other medication, which may interfere with the uptake.⁴⁸

Various groups use different methods to calculate RAIU.^{38,48} One of these is:

$$\% \text{ RAI uptake (RAIU)} = (A - B) / (C - D) \times 100$$

Where:

A = total counts per minute of the thyroid

B = total counts per minute of the thigh

C = total counts per minute of the thyroid phantom corrected for decay

D = total counts per minute of the room background corrected for decay

Normal thyroid uptake values have been quoted as 6-18% at 4 hours and 10 – 35% at 24 hours.⁴⁸

The values differ slightly from institution to institution.

2. ^{99m}Tc pertechnetate uptake

Technetium-99m pertechnetate uptake can also be used to evaluate thyroid function,^{10,39,49} as it is a good substitute for radioactive iodine (see Table 3.1). There is relatively high background activity in the neck and body at the time for optimal imaging (20 minutes after tracer administration). Therefore, a gamma camera method is used instead of the thyroid probe. Uptake can be calculated using the following method:²

Pre-injection and post-injection counts of the syringe of Tc-99m pertechnetate are acquired with the gamma camera. A thyroid scintigram is acquired 20 minutes after injection. Computer processing is

then carried out; regions of interest are drawn around the thyroid, thyroid background (neck), and the syringe images. Normalization of the syringe images for time, as well as normalization of the thyroid and background regions of interest for pixel size, is carried out. The following formula is used to derive the uptake value:

$$^{99m}\text{Tc-99m} \text{ pertechnetate percent uptake} = \frac{\text{Thyroid counts} - \text{Background counts}}{\text{Injected counts} - \text{residual counts}} \times 100$$

Normal thyroid uptake is quoted as 0.3 – 4.5%.

Visual assessment of uptake also helps the nuclear physician/technologist to estimate uptake even before this calculation is carried out, comparing uptake of activity in the thyroid with that of the salivary glands and with background activity. The hyperthyroid patient with Graves' disease often has much higher uptake in the thyroid compared to salivary glands and background. Nodular disease may present with normal to moderately increased thyroid uptake (see Table 3.2).

TSH receptor antibody assay

In cases where the diagnosis of Graves' disease is uncertain, measurement of the anti-TSH receptor antibodies may be helpful. However, it is not freely available in all centres and is expensive.³⁰ The assay serves as a marker for TSH receptor autoimmunity, especially in Graves' disease.⁵⁰

The functional assay measures the production or the accumulation of cyclic adenosine monophosphate (cAMP) by stably transfected Chinese hamster ovary cells with the human TSH receptor. The other type of assay is the competitive assay, which is not indicative of any functional activity of the antibody. Only functional assays can identify whether the antibody is agonistic [thyroid-stimulating antibody (TSAb)] or antagonistic [TSH stimulation blocking antibody (TSBAb)]. These TSBAb may be present in the same patients with stimulating antibodies, the effect of which is also inhibited, the overall activity being the algebraic sum of the two levels of activity.⁵¹ Some authors have discussed it as the appropriate diagnostic method for those patients with diffuse and patchy uptake on their thyroid scans. Some also say that it is an alternative to RAIU to confirm Graves' disease. However, it does not nullify the usefulness of the thyroid scan as all patients will require it to demonstrate the presence of cold nodules, which may have a higher risk of being cancerous. It is also useful for confirming the multinodular nature of goitre.^{30,52}

Further evaluation of the hyperthyroid patient depends on the findings in the individual patient. These include fine needle aspiration/biopsy, high-resolution thyroid ultrasound, and CT/MRI. These are incorporated into these patients' management.

Fine needle aspiration/ biopsy

In the hyperthyroid patient, it is indicated in further evaluation of thyroid nodules $\geq 1\text{-}2\text{cm}$.^{53,54} Utility of this procedure in hyperthyroid patients is in the exclusion of malignancy, in the cold nodule especially. Cold nodules may be due to colloid nodules, cysts, haemorrhage, inflammation, and cancer. Pathologic findings include benign adenomatoid nodules or lymphocytic thyroiditis, malignancy, follicular neoplasm, indeterminate nodules, or sample suspicious for carcinoma but insufficient for definite diagnosis.⁵⁵ Fifteen to twenty percent of cold and indeterminate nodules on a thyroid scan are likely to be malignant, hot nodules are less likely to be, with a risk of less than 1%.²

Accurate diagnosis depends on an adequate and representative sample interpreted correctly in the clinical context. False negatives could be due to poor specimens, cystic follicular variants of papillary carcinoma and follicular carcinoma. The false negative rate of thyroidal FNA has been quoted as $\leq 5\%$, and the false positive rate as 0 - 7.7%.⁵⁵

Thyroid ultrasound

Thyroid ultrasonography is not routinely performed in patients with hyperthyroidism. Its main role is in the assessment of thyroid nodules.⁵⁶

Other imaging modalities like ^{18}F -FDG PET, CT and MRI scans have little or no role in the routine management of the hyperthyroid patient. ^{18}F -fluorodeoxyglucose PET imaging can demonstrate functionality of the thyroid and assess thyroid nodules for malignancy. Nearly 50% of thyroid nodules discovered incidentally on FDG imaging were malignant.⁵⁶ Its limited availability and cost are against it being used as a routine tool for thyroid assessment.

CT and MRI are indicated to determine the extent of goitres, assess proximity of goitres to the trachea, as well as tracheal involvement while preparing patients for surgery. Both are also useful in volume estimation of irregular goitres.

MRI has been shown to be more precise than CT in the anatopographic evaluation of retrosternal goitre. Gadolinium-enhanced MRI in particular has been described as a suitable alternative to contrast-enhanced CT in the detailed evaluation of the anatomy of the neck, especially post-surgery.^{37,56,57}

CHAPTER 4
TREATMENT OF HYPERTHYROIDISM

As mentioned previously, hyperthyroidism can be treated using medication, surgery or radioisotope therapy. The mode of management varies with location of the treating physician; in Europe, Saudi Arabia and in Japan, medical treatment with antithyroid drugs is preferred as initial treatment, while in the United Kingdom, Belgium and the United States of America RAI would be the initial treatment of choice.¹¹ A more detailed description of these treatment modalities is rendered here.

Antithyroid drugs

Antithyroid drugs (ATDs) are derived from the thiourylene family, and comprise methimazole and propylthiouracil. Carbimazole is another example which is metabolized to methimazole. These drugs act by inhibiting iodine uptake, and by blocking the organification and coupling steps in thyroid hormone synthesis. Propylthiouracil, in addition, inhibits 5'-deiodinase I, thereby reducing the peripheral conversion of T4 to T3 in many extra-thyroidal tissues. Both drugs also cause immune suppression, which reduces the formation of stimulatory antibodies.¹⁹

Carbimazole is the more popular drug in Europe, while physicians in Japan and in the United States prefer to prescribe propylthiouracil.¹¹ In Nigeria, carbimazole is the only antithyroid drug available in the country. The same applies in the Western Cape region, where this study was carried out.

Both drugs are given orally; carbimazole in doses of 5-20 mg daily, and propylthiouracil 300-600 mg daily.

Indications for antithyroid drugs:⁵⁸

1. As primary therapy for hyperthyroidism from Graves' disease
2. To lower thyroid hormone levels before RAI therapy and surgery (the former especially in elderly patients and patients with cardiac comorbidity, to deplete the thyroid gland of stored hormone and reduce the risk of excessive post-treatment thyrotoxicosis from radiation thyroiditis)
3. In young patients with Graves' disease
4. In pregnancy

Remission is most likely to be achieved in patients with mild hyperthyroidism and small goitres.⁵⁹

When used as primary therapy, they are usually given for six months to two years. Long-term ATD therapy may lead to remission in some patients with Graves' disease.⁶⁰

Disadvantages of antithyroid therapy

1. Drug therapy may not be as successful in patients with toxic solitary thyroid nodules and multinodular goitres, as well as in severe biochemical hyperthyroidism.
2. Prompt recurrence may occur in more than 50% of treated patients; this figure is higher still after several years.⁶¹
3. Non-compliance is frequently an issue, and this affects the efficacy of disease control.
4. Both drugs have side-effects (0.003% incidence rate), which limit their usefulness, the most dreaded of which is agranulocytosis. Fortunately, this is rare, occurring in 0.001% of patients within three months of commencing treatment.^{3,6,62}
5. The cost of ATDs is another disadvantage. Patel et al calculated the cost per cure (defined as euthyroidism after one year of ATDs, and euthyroidism/hypothyroidism 2 years after RAI or thyroidectomy) as £ 1 375 (\$2 063) for patients treated with RAI, £3 763 (\$5644) for ATD-treated patients, and the highest was £6 551 (\$9 826) for patients who had thyroidectomy.⁶³

Surgical treatment of hyperthyroidism

Partial thyroidectomy is another method of treating hyperthyroidism. It was frequently used in the past for Graves' disease, but now is less commonly performed, except for the following reasons:

1. Very large or nodular goitre
2. Suspected co-existing thyroid cancer
3. Patients desiring definitive treatment but declining treatment with RAI

Disadvantages of surgical treatment^{6,60,61,64,65}

1. The patient requires hospital admission.
2. The procedure is fraught with significant post-operative morbidity and mortality: such as haemorrhage, hypoparathyroidism, and vocal cord paralysis.
3. Recurrence of hyperthyroidism and goitre may also occur.
4. Unsightly scars may develop.

Radioiodine-131 therapy of hyperthyroidism

The principle of using radioiodine-131 (RAI) as sodium iodide to treat hyperthyroidism is based on the fact that any thyroid tissue that produces thyroid hormone will trap and organify stable iodine or its radioisotopes. Once RAI is taken up by functioning thyroid tissue, delivery of locally destructive ionizing β -radiation occurs, after which cell death occurs over weeks to months.^{66,67} The unique

avidity of the thyroid gland for iodine makes RAI therapy a practical option for the treatment of hyperthyroidism.

Patient preparation⁶⁸

All patients who have chosen to receive RAI therapy should be given an explanation of the treatment, and informed signed consent for it should be obtained. These patients must discontinue the use of iodide-containing preparations; thyroid hormones and all medication that could potentially affect the ability of the thyroid to accumulate iodide should be stopped for a sufficient time before contemplated therapy.

Elderly patients and those at risk for developing cardiac complications may be pre-treated with ATDs prior to RAI therapy, especially if hyperthyroidism is severe, to deplete the gland of stored hormone. This minimizes the risk of exacerbation of thyrotoxicosis due to radiation thyroiditis.

Indications for RAI therapy

1. Primary treatment of hyperthyroidism due to Graves' disease, toxic multinodular goitre and solitary toxic nodule
2. Non-compliance with medical therapy
3. Disease refractory to medical or surgical therapy

Contraindications to RAI therapy⁶⁸

Absolute contraindications to RAI therapy are pregnancy and lactation, which does not apply to the male subjects being discussed in this study. Relative contraindications are as follows:

1. Unmanageable urinary incontinence
2. Uncontrolled hyperthyroidism
3. Active thyroid orbitopathy^{60,69,70}

There are several advantages of using RAI for treatment:

1. It is a beta-emitter whose β -particles deposit their radiation within a sphere of less than 1 mm from the decaying I-131 atoms.
2. In addition, it has γ -rays, which can be detected for imaging purposes.
3. Its half-life of eight days makes it appropriate for outpatient use.
4. The radiation delivered is enough to overcome the heterogeneity of the thyroid.
5. It is safe to use, and non-toxic. Various studies have proved that it has no effect on fertility, does not cause an increased incidence of congenital malformations, and does not increase the risk of cancer in treated patients or their offspring, above that of the general population.^{59,60,67,69}
6. Iodine-131 is readily available and affordable.

7. Its administration is simple, and the prescription is safe for patients known with iodine allergy because sub-physiological doses of RAI are given.⁶⁹
8. Treatment is on outpatient basis; hospitalization is not required.
9. Compliance is not an issue, since the dose of RAI is administered to the patient by the nuclear physician.
10. Treatment can be repeated, if necessary.

Determining the dose of radioactive iodine

There are different schools in determining the dose of RAI to be administered. Some people will use an empirical dose, others will use either a low or high fixed dose, while some will calculate the dose of I-131 to be administered. The most widely used formula to calculate such a dose, is:

thyroid dose (cGy) \times 0.037 \times thyroid mass (g)/effective half life of ¹³¹I (days) \times 17 \times 24h RAIU (%)

In an attempt to resolve the controversy over the use of empirical as against calculated doses, Jarlov et al conducted a study on 163 hyperthyroid patients who were treated with radioiodine-131 for diffuse goitre, toxic multinodular goitre and toxic adenoma using fixed and calculated doses. There was no significant difference in the outcome of therapy between the two treatment regimens.⁷¹

A small-pool syndrome has been described in hyperthyroid patients, in which 10-15% of these patients have a very fast thyroïdal turnover of iodine.⁴ Regarding patients with this “small pool” syndrome, Van Isselt and co-authors⁷² advocated that patients with Graves’ disease, who are scheduled for RAI therapy based on calculations of % RAIU, should have the % RAIU test performed as close to the time of therapy as possible. Rapid RAI turnover was noticed in 17% of the 5-hour RAIU tests, 19% of the 24-hour tests, and in only 9% of their patients on both the early and the late tests.

In 95% of patients treated with RAI or surgery, the degradation rate of radiolabelled thyroxine became normal or even subnormal compared to the previous rapid turnover.⁷³ The use of potassium iodide and low-dose antithyroid treatment in such patients has been studied in order to decrease the release of radiolabelled hormone and so limit the radiation dose to the patient as well as increase the residency time of RAI in the thyroid.^{74,75}

Toxic nodular goitre typically is more resistant to radioactive iodine therapy and frequently requires a larger dose.^{59,65,76} This is because of the heterogeneity in tracer uptake in the hot and cold areas.

It is not always possible to achieve the therapeutic ideal of euthyroidism while limiting hypothyroidism. Attempts to provide lower doses of radioiodine result in more frequent treatment failure or in persistent hyperthyroidism.^{77,78,79}

However, the rate of hypothyroidism after 10 years remains at least 50% irrespective of the treatment dose, because 2-3% of patients per year (from the second year onward) develop lymphocytic infiltration and tissue destruction.⁸⁰

Effectiveness of I-131 therapy

In a study of 100 hyperthyroid patients,⁸¹ thyroid volume reduction was found in all patients following treatment with RAI, but to a greater measure in patients with Graves' disease (mean reduction of 76%) and in patients with toxic adenoma (mean reduction of 69%). It was lowest in patients who had toxic multinodular goitres (mean reduction of 32%). The median activity received by the 86 patients who were cured was 555 MBq compared to 407 MBq received by the remaining 14 patients who remained hyperthyroid. The overall positive effect of RAI (definitive hypothyroidism or euthyroidism) was very high: 93.7% in the toxic adenoma group, 87.1% in patients with Graves' disease, and 81.1% in patients with multinodular goitre. The study concluded that RAI therapy is highly effective and safe for the control of hyperthyroidism.

Patients with toxic multinodular goitre experienced a 40% reduction in goitre size, as documented by Nygaard et al.⁸²

A retrospective study of 4473 hyperthyroid patients⁸³ showed that they were cured after an average of 1.7 doses. Eighty to ninety percent of patients with Graves' disease or toxic nodular goitre became euthyroid within 8 weeks after a single dose of RAI, while the remainder needed one or more additional doses. Fifty percent of the patients were cured by approximately 5 months, and 80% by one year following RAI treatment.

Functioning nodules co-existing with Graves' disease (Marine-Lenhart syndrome) will require higher doses of RAI to treat than are necessary for Graves' disease alone.⁸⁴

Effect of gender on outcome of therapy

The possible factors that could predict outcome of I-131 therapy have been studied in an attempt to optimize therapy: pretreatment with antithyroid medication, size of goitre, smoking and size of the dose administered.^{14,15,16,17}

Manji and associates⁸⁵ studied 2805 male and female patients. In this group, 2405 of them had Graves' disease and 400 had Hashimoto's thyroiditis. They were investigated for factors which could influence disease manifestation, such as age at diagnosis, gender, family history, smoking history and presence of goitre. A simultaneous analysis was performed on the influence of age, gender and presence of goitre on the biochemical severity of GD. This showed that presence of goitre was an independent predictor ($p < 0.001$), while age ($p = 0.54$) and gender ($p = 0.37$) were not. They concluded that there were "marked associations" between the following factors: age at

diagnosis, severity of disease, presence of goitre and ophthalmopathy, history of smoking and family history of thyroid disease, and disease manifestation. They advised that understanding these associations might improve the “tailoring of therapies”.

Although Tarantini et al⁸¹ found no influence of clinical parameters on clinical outcome, Allahabadia and colleagues¹³ discovered that their male patients had a significantly worse outcome than the females (67.6% cured after a single dose of RAI compared to 76.7%, $p = 0.02$), despite a reduced prevalence of palpable goitre in the former. This observation was even more marked in patients with Graves’ disease, where the cure rate with a single dose of radioiodine was only 52.2%, compared to 74.2% in females ($p < 0.001$). Male patients were more likely not to go into long-term remission with medical treatment and were more likely to require more than one dose of iodine-131 therapy. The incidence of hypothyroidism did not vary significantly between males and females (50.5% and 49.4%). These findings corroborated an earlier study also by Allahabadia et al¹², where male gender was a significant predictor of failure to enter remission after treatment with ATDs ($p < 0.01$), and of a requirement for multiple doses of RAI ($p = 0.02$).

Over a twenty-year study period, Bland and Hays¹⁸ studied 241 male patients and found that multiple doses of RAI were needed to treat 45% of these patients; these had more severe biochemical and clinical hyperthyroidism.

Side-effects of radioiodine-131 therapy

Commercial preparations of I-131 contain approximately 8 ng of iodine/37 MBq of activity so that the largest therapeutic doses have less iodine than the daily diet. Therefore it is safe for patients who have iodine allergies.⁶⁹

1. Hypothyroidism following treatment with RAI:

This is a common effect observed after radioiodine therapy and often considered the desired therapeutic effect. In the study on hyperthyroid males quoted previously, Bland and Hays found that younger male patients had a longer period of time before becoming hypothyroid, and up to 71% eventually became hypothyroid 15 years post-therapy¹⁸ After 20 years of follow-up of 346 patients treated for a toxic solitary nodule, Ceccarelli et al⁸⁶ found that 60% became hypothyroid. Initially, 7.6% were hypothyroid after the first year, 28% by 5 years, and 46% by their tenth year of follow-up. Factors increasing the risk of hypothyroidism were patient age, %RAIU values, and pre-treatment with methimazole. The value of the last factor in predicting the development of hypothyroidism depended on the degree of suppression of extranodular thyroid tissue.

Permanent hypothyroidism is the main complication of radioiodine therapy for hyperthyroidism, occurring by the first year post-treatment in at least 50% of patients who were given high doses of

activity and in at least 50% of those given lower doses by 25 years.^{87,88} Treatment of hypothyroidism is with thyroid hormone supplementation, which will be discussed later.

2. Radiation thyroiditis:

Transient pain in the thyroid, following RAI, has been reported. This resolves with the use of anti-inflammatory drugs.⁸⁹

3. Exacerbation of Graves' ophthalmopathy:

Wagner and co-authors⁶⁹ proposed that this phenomenon is due to the release of antigens from the thyroid gland, shared by the thyroid and the orbit, into the circulation following radiation injury, which causes subsequent worsening of the autoimmune reactions. Other authors have also documented this side-effect, especially among patients who are smokers.^{70,90,91} Sridama and De Groot⁹¹ found severe ophthalmopathy to the same degree in patients treated with radioiodine as those treated with antithyroid medication or surgery. On the other hand, Talledst et al⁹² have described exacerbation of ophthalmopathy in 33% of radioiodine-treated patients, 16% of those surgically treated and in 10% of those on medical therapy. However, a cause and effect relationship could not be established. Graves' ophthalmopathy essentially follows a course independent of the treatment of disease, but patients with clinically evident thyroid eye disease are prescribed a three-month treatment with oral prednisone, especially if other risk factors for developing ophthalmic complications (such as smoking) are present.^{70,77,90} Chemosis was also reported in 16.6% of patients in the study on hyperthyroid males, following doses of 5000-6000 rads to the thyroid.⁹⁰

4. Secondary neoplasms:

A number of studies done on hyperthyroid patients treated with RAI demonstrated no increase in the incidence of leukaemia or other neoplasms,^{93,94,95,96} and no evidence for genetic defects in children.^{97,98,99,100} Saenger and co-workers found no difference in the incidence of leukaemia among hyperthyroid patients treated by radioiodine, antithyroid therapy, or with surgery.⁹⁵

However, Metso and co-workers¹⁰¹ in a large study population demonstrated a significant increased incidence of cancer above the general population, especially of the breast, stomach and the kidneys. Therefore, it is possible that there are other factors responsible for the higher incidence of secondary cancers seen in certain study populations and not in others.

5. Recurrent laryngeal nerve damage has been reported but RAI therapy could not be verified as its cause.⁷⁰

6. Both hypo- and hyperparathyroidism have also been documented, but the authors concluded that they were probably not caused by radioiodine therapy.⁶⁹

Adjuncts to therapy for hyperthyroidism: beta-blockers

This class of drugs is used as adjunct to all three kinds of treatment of hyperthyroidism for rapid symptomatic control, as part of pre-operative patient preparation to render the thyroid less vascular, and in the management of thyroid storm. The mechanism of action is the blockade of β -adrenergic receptors; beta-blockers also decrease the peripheral conversion of T_4 to T_3 .¹⁰² The latter effect is apparently insignificant, as the drug does not produce a significant effect on blood thyroid hormone levels. Drugs without an intrinsic sympathomimetic action are preferred, such as propranolol, which is usually administered in oral doses of 40-80mg eight-hourly. These are contra-indicated in asthmatic patients, in whom they could stimulate bronchospasm.^{62,103}

Thyroid supplements

Patients may need thyroid hormone replacement therapy following radioiodine therapy if they develop hypothyroidism.⁵⁹ Therefore, patients could begin to receive partial doses of levothyroxine approximately two months after treatment. The final thyroid replacement dose must be individualized. TSH is not a good indicator of the patient's thyroid status as it takes weeks to several months before it normalises after thyroid supplementation.⁵⁹ Free thyroid hormones are more accurate than TSH during this period. Prompt thyroid hormone replacement produces a minimum of morbidity and mortality.⁵⁹

In conclusion, considering the different options available for treating hyperthyroidism, radioiodine therapy is the most effective and convenient method of achieving long-term control of this disease, which is also safe and simple to administer.^{6,13,70,80}

CHAPTER 5
MATERIALS AND METHODS

Subjects of the study

A retrospective analysis was done of the pre-therapy characteristics and post-therapy outcome of all male patients who were treated with radioactive iodine (I-131) for hyperthyroidism at Tygerberg Hospital from June 1988 – July 2007.

Patient data were retrieved from the Nuclear Medicine thyroid clinic electronic database. Further information was obtained from patient folders in the thyroid clinic and from hospital folders. The study was approved by the Committee for Human Research of the Stellenbosch University. Patients with deficient records, e.g. incomplete patient records, were excluded.

Patient follow-up and outcomes

For those patients with insufficient follow-up records, efforts were made to contact them by telephone. Referring physicians were also contacted in an effort to get thyroid function results. Further efforts at updating the database were made through the Chemical Pathology thyroid function database of the Tygerberg Hospital. Despite all these efforts, follow-up remained a problem.

Evaluation of the database was done using pre-treatment variables (patient age, diagnosis at presentation, Tc-99m pertechnetate uptake, and serum free thyroid hormone concentration), doses of RAI administered, post-treatment serum free thyroid hormone concentration, timing of visit and treatment outcome (categorized as euthyroid, hypothyroid and hyperthyroid).

For the purposes of this research, cure was perceived as hypothyroidism or euthyroidism at 3 months after receiving RAI. This 3-month period was chosen as there was a limitation in the form of poor follow-up records. Patients with T4 and T3 values within normal limits but with TSH values less than 10 IU/l (subclinical hypothyroidism) were regarded as euthyroid, while similar patients with TSH values greater than 10 IU/l were classified as being hypothyroid and placed on thyroxine supplementation as for overtly hypothyroid patients.^{59,104,105,106}

Data management and statistical analysis

The patient data used in this study was collected from clinic folders and Microsoft Access spreadsheets and transferred to Microsoft Excel spreadsheets. Statistical analysis of data was done using Microsoft Excel by the candidate, and a University statistician was consulted, who conducted more detailed analysis using Statistica 8.0.

Analysis of variance (ANOVA) was used to assess the relationship between continuous and categorical data. If the residuals were not normally distributed, the results were confirmed using the Mann-Whitney U test or the Kruskal-Wallis rank-sum tests. Discrepancies between parametric and non-parametric analyses were reconciled using a bootstrap multiple comparisons procedure.¹⁰⁷

Comparison of categorical data was done using contingency tables with the maximum likelihood chi-square test.

A population of female hyperthyroid patients was also compared to the male population. The two populations were matched according to the following parameters:

- a. Age: Less than 20 years, 20-34years, 35-49 years, ≥ 50 years
- b. Diagnosis at presentation: Graves' disease (GD), toxic multinodular goitre (TMG), toxic solitary nodule (TSN)
- c. Tc-99m pertechnetate uptake values: Less than 4%, 4-9%, 10-19%, and $\geq 20\%$
- d. First dose of RAI: Less than 250 MBq, 250-399 MBq, and ≥ 400 MBq

CHAPTER 6
RESULTS

Of 365 male patients in the database, 308 were eligible for the study; others did not attend further clinic appointments, or had been referred back to their referring physicians after receiving RAI (as was the practice with some physicians rotating through the Thyroid Clinic when patients had difficulty with transport due to the distance of their homes from the hospital), or had incomplete data. Patient attendance continued to drop with longer time intervals after the administration of the RAI, owing to defaulters as well as discharges to referring physicians or to patient's local community health clinic in cases where patients came from afar and transportation was a problem. This is reflected in the attendance rates quoted for the 3- and 6-month follow-up visits.

Two hundred and sixty-six patients (86.4%) had Graves' disease (GD), 35 (11.3%) were diagnosed as having toxic multinodular goitre (TMG) and the remaining 7 (2.3%) had toxic solitary nodules (TSN). (Fig. 6.1)

Two hundred and fifty-nine patients (84.1%) were treated with a single dose of RAI, while 49 (15.9%) required further doses. A second dose had to be administered to 38 patients, while 8 received 3 doses, 2 got 4 doses and 1 patient had 5 doses in all (these included a first dose received prior to referral to our Thyroid Clinic).

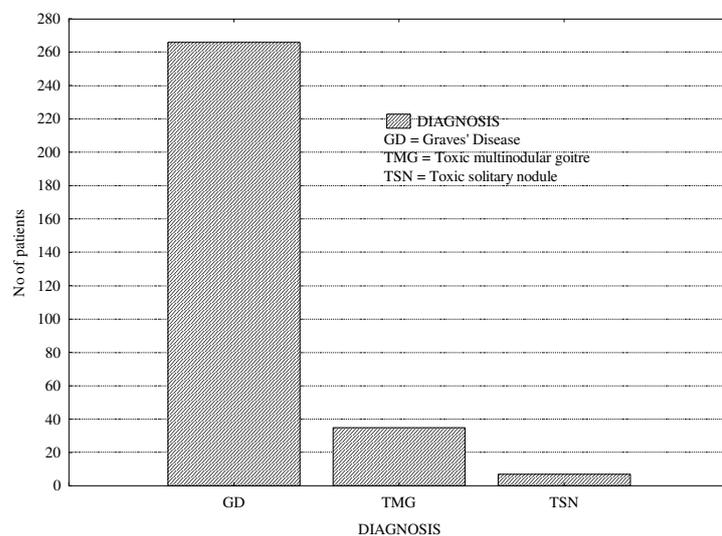


Fig. 6.1: Graphical representation of patients grouped according to diagnosis at presentation

Table 6.1 and Fig. 6.2 summarize the baseline characteristics of the patient group. The mean age of the men was 44 ± 13.6 years (range 14-77 years). Patients with GD were predominantly in the younger age groups, while those with toxic nodular goitres were in the older range.

The average pre-treatment T4 value was 68.9 ± 31.8 pmol/L (range 5.7 – 155 pmol/L); while the mean Tc-99m pertechnetate uptake value was $15.8 \pm 10.9\%$ (range 0.88 - 62.9).

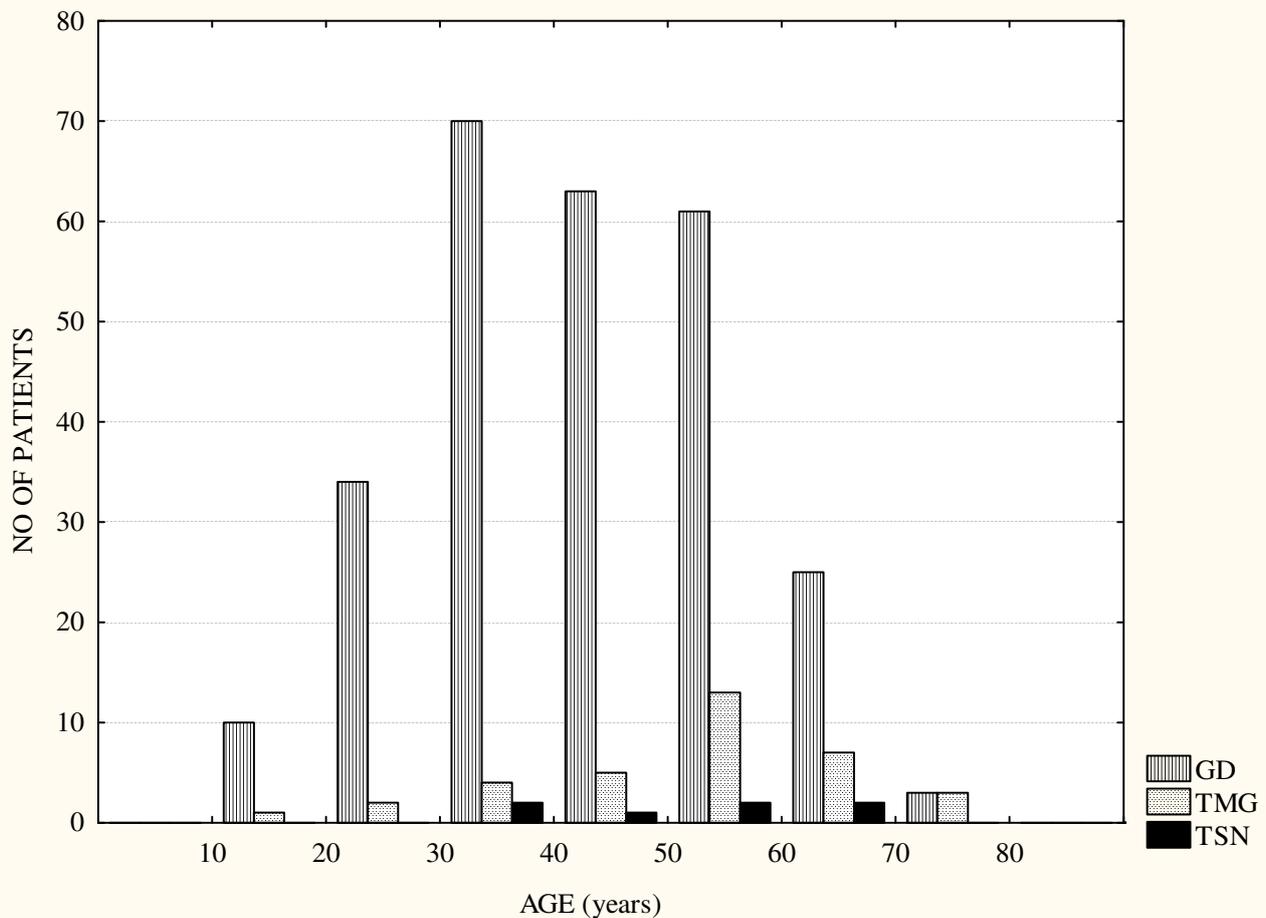
Patients with GD presented with more severe hyperthyroidism than the other patients; mean free T4 of 71.9 ± 31.1 pmol/L compared to 51.4 ± 29.9 pmol/L for the TMG group of patients, and 39.6 ± 26.8 pmol/L for the TSN group (ANOVA $p < 0.0001$, confirmed by the Kruskal-Wallis test). Patients with nodular goitre were treated with higher doses than patients with GD.

Table 6.1: Baseline characteristics of male hyperthyroid patients

PARAMETER	GD n = 266	TMG n = 35	TSN n = 7
Age at presentation (years)			
Mean \pm SD	43.2 \pm 13.1	52.4 \pm 14.7	50.05 \pm 13.4
Range	15-77	14-77	31.6-65
Baseline free T4 (pmol/L)			
Mean \pm SD	71.9 \pm 31.1	51.4 \pm 30	39.6 \pm 26.8
Range	11.5-155	5.7-130	16.4-95.1
Baseline free T3 (pmol/L)			
Mean \pm SD	26.3 \pm 10.1	17.3 \pm 11.4	13.1 \pm 5.6
Range	3.7-44	3.3-48	7-21.7
Baseline Tc-99m PU* (%)			
Mean \pm SD	16.8 \pm 10.8	10.16 \pm 10.3	6.3 \pm 5.1
Range	1.2-62.9	0.88-41.4	3-17.7
First dose RAI (MBq)			
Mean \pm SD	325.1 \pm 69.3	349.3 \pm 88.5	428.1 \pm 28.6
Range	186-487	201-502	391-458

PU= pertechnetate uptake

GD= Graves' disease, TMG = toxic multinodular goitre, TSN = toxic solitary nodule

Figure 6.2: Histogram of age according to scan diagnosis

At the first 3-month appointment following therapy, 237 patients were seen; 181 patients had been cured (76.4%), with normal or low free thyroid hormone levels, while 56 remained hyperthyroid (23.6%). Tables 6.2 and 6.3 summarize these findings.

Six months after therapy, 132 patients attended the clinic for evaluation; 56 patients had low thyroid hormone values, 31 had thyroid function results within normal limits, and 45 patients had high free thyroid hormone levels. Thus, of these 132 patients, 65.9% had been cured. Subsequent follow-up visits dwindled substantially from 9-12 months and upwards; from 34 patients at the 9-month visit to 7 patients at the 21-month visit.

Further evaluation of the patients was performed using data for the 3-month follow-up visit.

Table 6.2: Post-treatment characteristics of male hyperthyroid patients

PARAMETER	GD n = 266	TMG n = 35	TSN n = 7
Patient outcome (% of dose group)			
Single doses (n = 259)	224 (86.5%)	28 (10.8%)	7 (2.7%)
Multiple doses (n = 49)	42 (85.7%)	7 (14.3%)	0
Number of patients at first 3-month visit (n = 237)	203 (85.7%)	28 (11.8%)	6 (2.5%)
Patient number (% of 3-month follow-up, n = 237)			
Euthyroid at 3 months (n = 36)	28 (11.8%)	5 (2.1%)	3 (1.3%)
Hypothyroid at 3 months (n = 145)	129 (54.4%)	14 (5.9%)	2 (0.8%)
Hyperthyroid at 3 months (n = 56)	46 (19.4%)	9 (3.8%)	1 (0.4%)

GD= Graves' disease, TMG = toxic multinodular goitre, TSN = toxic solitary nodule

Table 6.3: Post-treatment characteristics of male hyperthyroid patients, comparing outcome of each diagnostic group

PARAMETER	GD n = 266	TMG n = 35	TSN n = 7
Patient outcome (% of diagnostic group)			
Single doses (n = 259)	224 (84.2%)	28 (80%)	7 (100%)
Multiple doses (n = 49)	42 (15.8%)	7 (20%)	0
Number of patients at first 3-month visit (n = 237)	203 (76.3%)	28 (80%)	6 (85.7%)
Patient number (% of 3-month follow-up, n = 237)			
Euthyroid at 3 months (n = 36)	28 (13.8%)	5 (17.9%)	3 (50.0%)
Hypothyroid at 3 months (n = 145)	129 (63.5%)	14 (50.0%)	2 (33.3%)
Hyperthyroid at 3 months (n = 56)	46 (22.7%)	9 (32.1%)	1 (16.7%)

GD= Graves' disease, TMG = toxic multinodular goitre, TSN = toxic solitary nodule

The study group of male patients was compared with a matched group of female patients from the Nuclear Medicine Thyroid Clinic database. Table 6.4 summarizes the post treatment characteristics of the matched female group. The patients were matched for age at presentation, diagnosis (Graves' disease, toxic multinodular goitre or toxic solitary nodule), the baseline pertechnetate uptake and the first dose of RAI administered. Tables 6.6 to 6.8 summarise the findings of these comparisons.

Table 6.4: Post-treatment characteristics of female hyperthyroid patients, comparing outcome of each diagnostic group

PARAMETER	GD n = 1025	TMG n = 204	TSN n = 13
Patient outcome (% of dose group)			
Single doses (n = 1079)	892 (82.7%)	174 (16.1%)	13(1.2%)
Multiple doses (n = 163)	133 (81.6%)	30 (18.4%)	0
Patient number (% of 3-month follow-up, n = 1242)			
Euthyroid at 3 months (n =)	192 (15.5%)	69 (5.6%)	11 (0.0%)
Hypothyroid at 3 months (n =)	639 (51.5%)	46 (3.7%)	1 (0.0%)
Hyperthyroid at 3 months (n =)	194 (15.6%)	89 (7.2%)	1 (0.0%)

GD= Graves' disease, TMG = toxic multinodular goitre, TSN = toxic solitary nodule

An interesting observation was that increasingly higher doses of RAI were administered over the consecutive years. In figure 6.3, the male doses are compared with those of the females from 1989-2006. The year 2007 was not included, because the female data for 2007 were not yet available in the database.

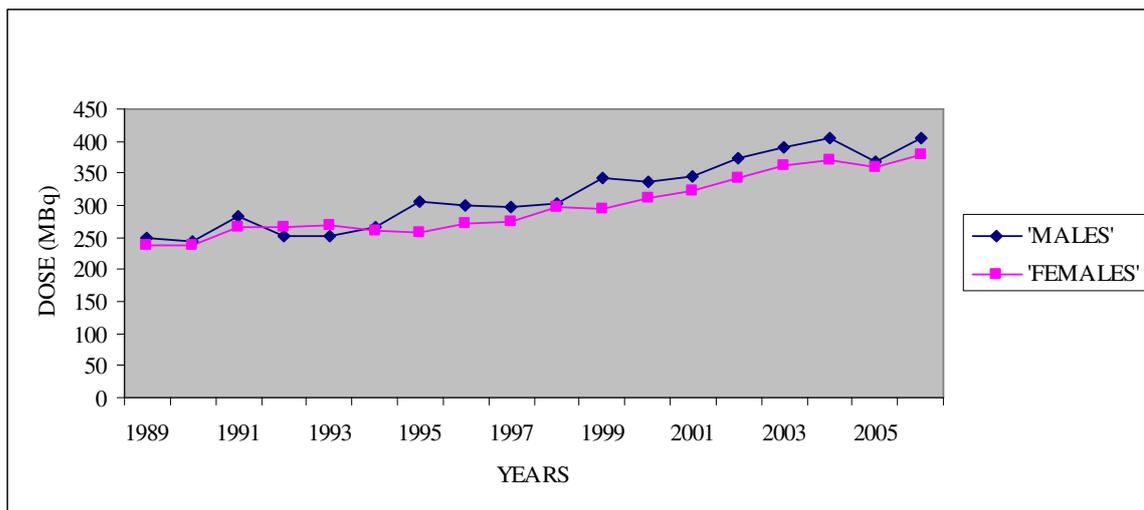


Fig. 6.3: Graphical representation of administered doses of RAI from 1989-2006

Applying the Bonferroni test, the difference in the average administered doses of RAI over the years only became statistically significant in 1998. The average doses were therefore also combined

into two groups, namely 1989 to 1998 (pre-1999) and 1999 to 2006 (post-1998). Figure 6.4 illustrates the difference in the administered dose of RAI in the two year groups, for the male and female patients. There is a significant difference between the average doses in the two year groups. The dose difference between males and females are more marked in the post 1998 year group ($p < 0.005$).

Fig.6.4: Comparison of the average dose of RAI administered to male and female patients in the year groups pre-1999 and post-1998

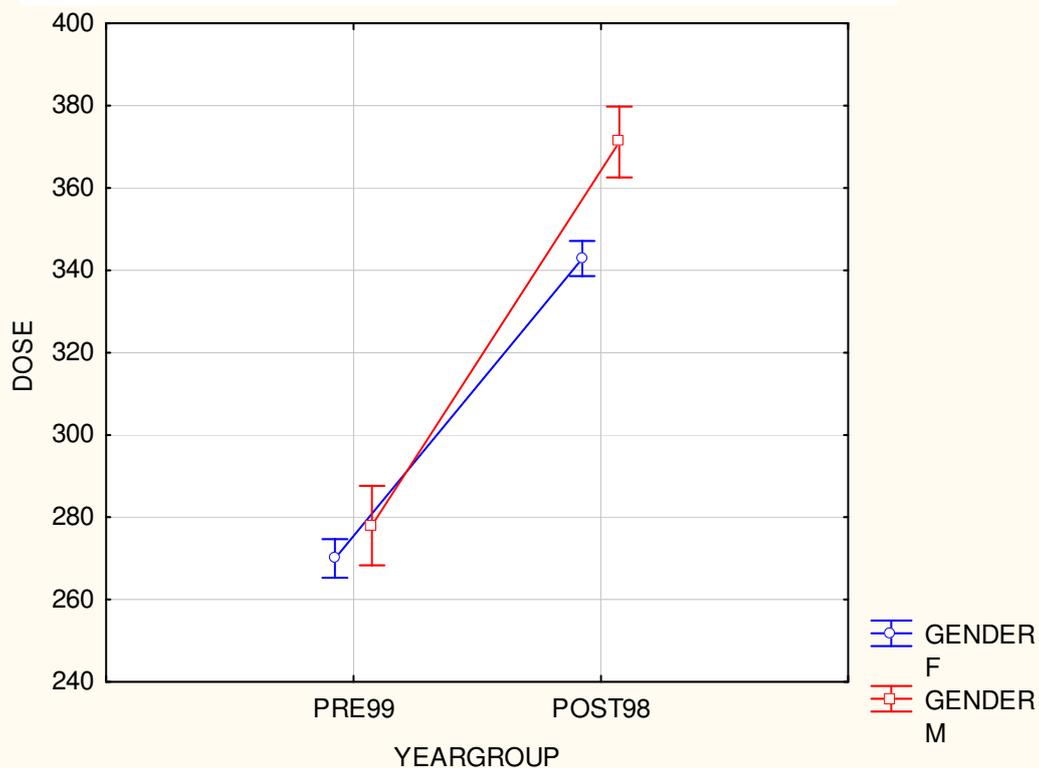


Table 6.5 compares the outcomes of the two patient groups in the pre-1999 and post-1998 year groups. There is no difference in the outcomes of the male patients ($p = 0.8$), in spite of the significantly higher doses administered to men. In contrast, a statistically significant difference between the two year groups were found in females ($p < 0.0001$).

Table 6.5: Comparison of the outcomes in male and female patients in the year groups pre-1999 and post-1998

		Euthyroid	Hypothyroid	Hyperthyroid
Males	Pre-1999	4 (3.1%)	73 (56.6%)	52 (40.3%)
	Post-1998	5 (3.2%)	84 (52.8%)	70 (44.0%)
Females	Pre-1999	62 (10.7%)	346 (60.1%)	168 (29.2%)
	Post-1998	141 (20.2%)	403 (57.8%)	153 (22.0%)

Table 6.6: Comparison of the dose of RAI in MBq administered to male and female patients for different baseline parameters

		FEMALES (N)	MALES (N)	P VALUE (ANOVA)
AGE	<20 yrs	267 ± 48 (26)	251 ± 36 (8)	0.40
	20-34 yrs	291 ± 56 (307)	320 ± 72 (60)	0.0005
	35-49 yrs	301 ± 57 (543)	345 ± 60 (77)	<0.0001
	≥50 yrs	337 ± 79 (366)	338 ± 78 (92)	0.91
DIAGNOSIS	GD	299 ± 59 (1025)	329 ± 69 (203)	<0.0001
	TMG	351 ± 80 (204)	340 ± 87 (28)	0.52
	TSN	426 ± 103 (13)	425 ± 30 (6)	0.97
TcO ₄ UPTAKE	<4%	344 ± 91 (164)	333 ± 80 (32)	0.53
	4-9%	297 ± 63 (293)	317 ± 77 (62)	0.04
	10-19%	299 ± 59 (373)	333 ± 61 (74)	<0.0001
	≥20%	311 ± 61 (412)	347 ± 73 (69)	<0.0001

GD = Graves' disease, TMG = toxic multinodular goitre, TSN = toxic solitary nodule

a. Age

Male patients in the study group received statistically significantly higher first doses of RAI compared to female patients in the age categories of 20-34 years ($p = 0.0005$), and 35-49 years ($p < 0.0001$). No difference was found for the younger patients <20 years ($p = 0.40$) and those older than 50 years ($p = 0.91$).

b. Diagnosis

The dose of RAI administered to male patients with GD was significantly higher than that for female patients ($p < 0.0001$). There was no significant difference between male and female genders for the first dose administered to patients with TMG ($p = 0.52$) or TSN ($p = 0.97$).

c. Tc-99m pertechnetate uptake

If the first dose of RAI is compared to the pertechnetate uptake, male patients received significantly higher doses than the females in all the categories with increased uptake. This difference was even more pronounced in patients with pertechnetate uptake >10%.

Table 6.7: Comparison of baseline pertechnetate uptake, and free T4 and free T3 values at baseline and three months follow-up for males and females in different administered RAI dose categories

			FEMALES (N)	MALES (N)	P VALUE (MW)
<250 MBq	PU	Baseline	15.1 ± 11.4 (220)	12.4 ± 11 (29)	0.05
		T4	63 ± 26 (220)	61 ± 24 (29)	0.64
		3 months	12.4 ± 19.7 (215)	22.1 ± 24.8 (29)	0.02
	T3	Baseline	23 ± 10 (218)	22 ± 10 (27)	0.56
		3 months	5.9 ± 8.4 (213)	9.1 ± 9.1 (29)	0.01
	250 – 399 MBq	PU	Baseline	17.5 ± 11.8 (899)	15.1 ± 9.6 (165)
T4			71 ± 31.4 (899)	66.6 ± 29.7 (165)	0.11
		3 months	15.6 ± 20.8 (891)	14.1 ± 22.7 (163)	0.005
T3		Baseline	26.2 ± 26.3 (883)	24.5 ± 10.6 (157)	0.26
		3 months	6.0 ± 7.8 (879)	6.0 ± 11 (160)	0.11
≥400 MBq		PU	Baseline	13.3 ± 12 (123)	19 ± 13.9 (43)
	T4		50.9 ± 30.7 (123)	70.1 ± 41.2 (43)	0.01
		3 months	16.6 ± 14.4 (123)	15.6 ± 18.6 (43)	0.03
	T3	Baseline	17.8 ± 9.8 (121)	24.3 ± 11.5 (43)	0.002
		3 months	6.1 ± 5.8 (121)	5.4 ± 6.0 (41)	0.16

PU – pertechnetate uptake MW = Mann-Whitney U test

Table 6.8: Comparison of free T4 and free T3 values of males and females at three months follow-up in different baseline pertechnetate uptake categories

TcO ₄ ⁻ UPTAKE		FEMALES (N)	MALES (N)	P VALUE (MW)
<4%	T4	16.3 ± 19.4 (164)	18.0 ± 24.3 (32)	0.81
	T3	5.7 ± 5.8 (163)	5.3 ± 6.7 (31)	0.39
4 – 9%	T4	13.0 ± 15.2 (289)	13.2 ± 20.3 (61)	0.06
	T3	4.8 ± 5.3 (286)	5.4 ± 7.6 (62)	0.63
10 - 19%	T4	12.8 ± 16.6 (370)	14.4 ± 22.3 (73)	0.94
	T3	5.0 ± 6.5 (356)	6.9 ± 14.0 (69)	0.67
≥20%	T4	18.3 ± 25.2 (406)	17.0 ± 23.5 (69)	0.3
	T3	7.8 ± 9.8 (408)	7.0 ± 8.9 (68)	0.31

MW – Mann-Whitney U test

d. Doses of RAI

Female patients who belonged to the groups of those who had received <250 MBq, and 250-399 MBq, had higher Tc-99m pertechnetate uptake than the males in these same groups (Mann-Whitney p-values = 0.05, 0.05, respectively), while male patients who were administered doses greater than 399 MBq had higher pertechnetate uptake than their female counterparts (Mann-Whitney p = 0.008).

A significant difference existed between the two gender groups for the 3-month outcome; male patients who had received RAI doses <250 MBq had higher free T4 (Mann-Whitney $p = 0.02$) and higher T3 values (Mann-Whitney $p = 0.01$) than the females. However, at higher doses, the female patients had higher free T4 results.

None of the baseline variables of age, T4 and T3, and first dose of RAI was a significant predictor of free T4 at 3 months (Table 6.9).

Table 6.9: Depiction of significance of baseline patient parameters and dose as predictors of outcome (T4 at 3-month follow-up visit)

	Spearman regression p-value for parameters				
	Age	Baseline T4	Baseline T3	Baseline TSH	Dose of RAI
3T4	0.79	0.37	0.12	0.54	0.59

An assessment of the relationship between free thyroid hormone levels and the number of doses administered showed that patients who were more severely hyperthyroid (based on free T4 and free T3 values (figure 6.4) and the Tc-99m pertechnetate uptake (figure 6.5) were more likely to receive multiple doses RAI.

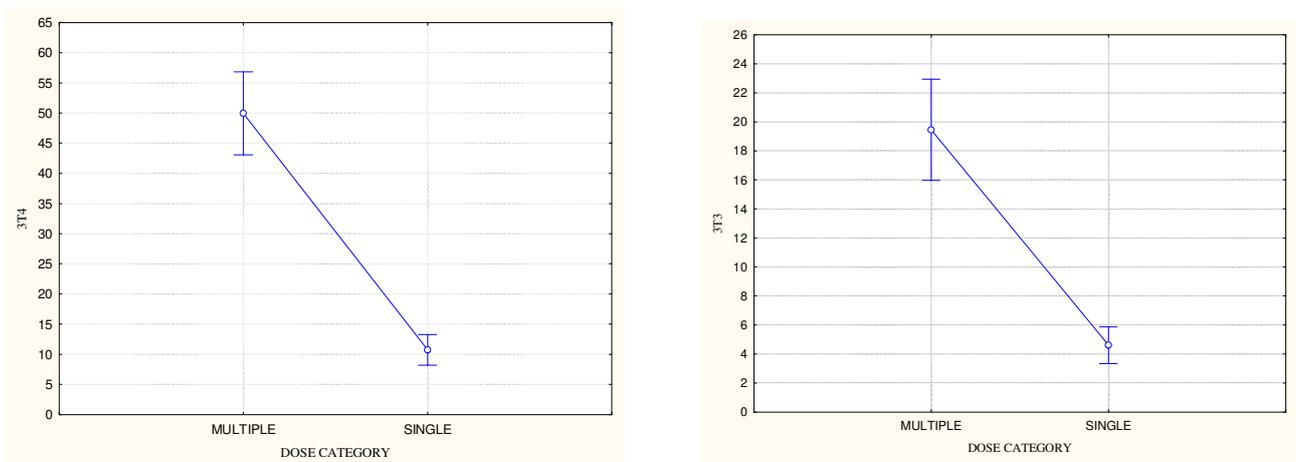


Fig. 6.5: Relationship between probability of single or multiple dosing, and the mean free T4 and mean free T3 values at 3 months ($p < 0.0001$ both for T4 and T3)

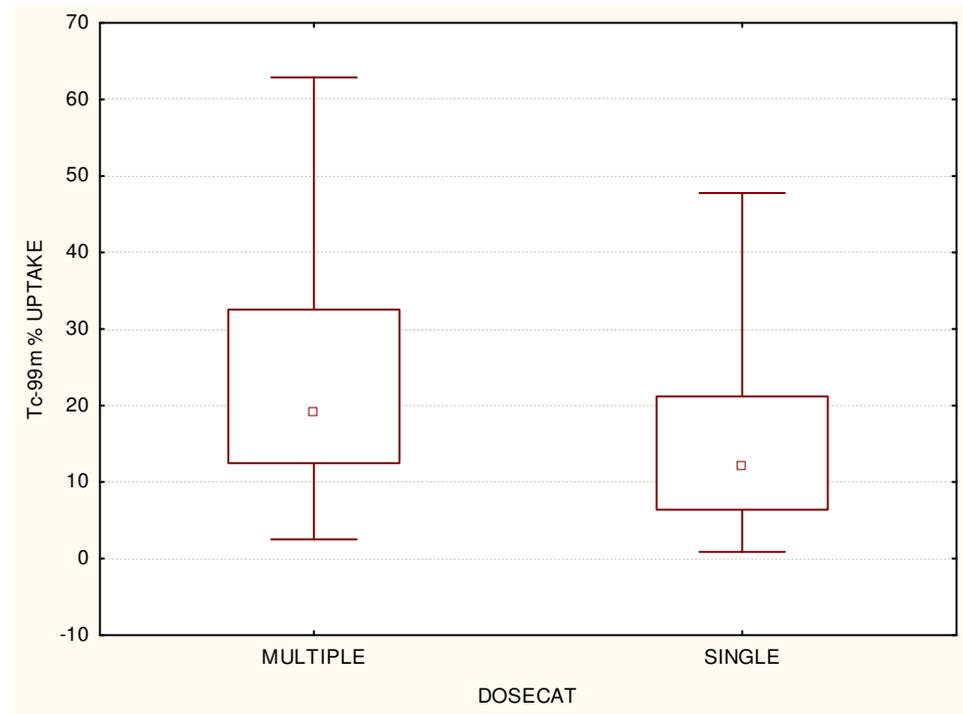


Fig. 6.6: Relationship between Tc-99m pertechnetate uptake and the probability of receiving single or multiple doses of RAI, $p = 0.0002$)

CHAPTER 7
DISCUSSION AND CONCLUSION

At the Tygerberg Nuclear Medicine thyroid clinic, an empirical approach was adopted for calculating the dose of RAI, taking into consideration factors such as patient findings (age, personal circumstances), the severity of hyperthyroidism (based on clinical findings, TFT, Tc-99m pertechnetate uptake), thyroid morphology (e.g. nodular goitre or Graves' disease), and gender. An element of this approach was that male patients were considered to be more resistant to RAI treatment, and a higher RAI dose would therefore be administered. Patients being retreated would also receive higher doses compared to otherwise similar patients. The purpose of this research was to test the assumption that men are more resistant to RAI therapy than women.

The regimen in use at the Nuclear Medicine Thyroid Clinic attempts to avoid a prolonged thyrotoxic state in our patients (and the attendant symptoms) without rendering the patients hypothyroid. The avoidance of low-dose regimens should reduce the incidence of re-treatment, which is said to worsen ophthalmopathy and may render the thyroid more radio-resistant.⁸⁹ The other regimen is to administer high doses of RAI, aiming at hypothyroidism as the intended outcome. Compared with results obtained from regimens using higher doses, more of our patients were still hyperthyroid following RAI.

The routine practice at the Tygerberg Nuclear Medicine thyroid clinic was that patients were followed up at the Nuclear Medicine Thyroid Clinic until they became euthyroid or hypothyroid, with the thyroxine dose titrated according to their T3 and T4 levels, because the response of TSH to hormone supplementation lags behind that of the thyroid hormones.⁵⁹ While euthyroidism would be desirable, hypothyroidism is an expected outcome.⁴⁴ This practice was not followed in all cases, owing to other factors such as difficulty in returning for follow-up owing to the fact that patients lived at extreme distances from the hospital, and due to transport problems. Therefore, the doctor rotating through the clinic at the time may have discharged patients from the clinic back to their referring physician after they had received the RAI capsule. This practice compromised our ability to follow-up these patients.

The cure rate of 76.4% in our study of 308 men is lower than those quoted in previous studies, although it must be noted that we are reporting on a 3 month follow-up period. Berg et al⁹³ in a retrospective study of 91 men and 475 women with GD and TMG found a cure rate of 93%. In two hundred and forty-one men studied by Blahd and Hays¹⁸ a cure rate of 85% within 10 months after a single dose of RAI was described, while only 25% of patients who needed more than one dose of RAI, became euthyroid in the same period. Allahabadia et al¹³ showed a cure rate of 84.6% 6 months after a single dose of 370MBq in 370 patients. On the other hand, the males in their group had a significantly lower cure rate after one dose of RAI, than females ($p = 0.02$). Nordyke and Gilbert⁷⁹ had a similar cure rate to ours of 76.2% in 605 patients with GD. In their study,

per technetate uptake above 18%, size of goitre above 70g, and the TSH level were significantly associated with outcome. Age and duration of pretreatment with ATDs were not significant factors. In an earlier study of 536 hyperthyroid patients with GD reported by Allahabadia et al,¹² the 92 male hyperthyroid patients had a much lower cure rate (47%) than those in our study group.

We performed a comparative analysis of the male patients with a female group matched for age, diagnosis, Tc-99m per technetate uptake, and first dose of RAI, in order to assess the influence of gender on treatment outcomes. This comparison of the outcome of RAI therapy in our male and female groups of hyperthyroid patients showed that males received significantly higher first doses of RAI than females in patients aged 20-49 years, those with Graves' disease and with per technetate uptake higher than 4%. Although the mean T4 levels at 3 months post therapy were statistically significantly lower in men who received more than 250 MBq RAI, the same was not true for the free T3 levels. The differences in the T4 levels are most probably not clinically significant (15.6 ± 20.8 in females versus 14.1 ± 22.7 in males).

We observed that increasingly higher doses of RAI were administered over the consecutive years. When comparing the outcomes during the earlier years of our study with the later period, the increase in the dose to males was more significant than in the females. In spite of this, the outcome in the men was not significantly different. Although the percentage of men who were still hyperthyroid was slightly higher, and the percentage becoming hypothyroid slightly lower, these differences were not statistically significant. This may strengthen the assumption that men are more resistant to RAI therapy than females.

The similarity in outcome between male and female patients over 50 years of age was probably due to the practice of administering higher doses to patients with nodular goitre, who also tended to be older. The relatively higher dose of RAI administered to male patients with GD is not unexpected, as that was the practice in our thyroid clinic.

A difference in cure rates between men and women with Graves' disease was seen in the study conducted by Nordyke and Gilbert⁷⁹, even though the difference in cure was not statistically significant (chi square, $p = 0.12$). There was a direct relationship between cure and dose in the range of 185-370 MBq.

In a second study of 813 patients (170 males and 643 females) by Allahabadia and his co-workers,¹³ higher dose (370 MBq as against 185 MBq), female gender, age greater than 40 years, less severe hyperthyroidism, and small size of goitre were all factors that favoured cure after a single dose of RAI. They therefore suggested larger doses for male patients, those with more severe hyperthyroidism and medium- and large-sized goitres.

We observed that male patients who received RAI in doses <250 MBq had significantly higher T4 and T3 values 3 months post-therapy than their female counterparts. This response to a relatively

low dose of RAI may support the theory that male patients require higher doses compared to females. Also, the more hyperthyroid patients were, the more likely they were to need multiple doses of RAI.

Using the empirical dose regimen, more than half of our study population was hypothyroid at the 3- and 6-month visits. Hypothyroid patients were placed on thyroxine supplements (Eltroxin®) and the dose titrated according to clinical and biochemical findings.

The ideal dose prescription for RAI therapy should cure hyperthyroidism (render patients euthyroid or hypothyroid), preferably with one dose and no side effects.⁶⁴ Iagaru and McDougall¹⁰⁸ state that “the dose of ¹³¹I should be sufficient to cure hyperthyroidism in a reasonable time (< 6 mo), and both patients and physicians should recognize and accept that thyroid hormone replacement will be required.” The perfect method for determining such a dose does not exist as yet. Low-dose regimens lead to repeated treatment, and protracted periods of hyperthyroidism. Higher doses tend to render the patient hypothyroid, requiring thyroid hormone supplementation.⁶⁹ The use of calculated or empirical doses of RAI may not affect outcome of therapy.¹⁰⁹

Numerous studies have been conducted in order to discover the factors that determine the outcome of therapy with RAI.^{110,111,112,113} Bland and Hays¹⁸ treated their group of 241 men with calculated doses of RAI (mean dose 205.7 ± 109.5 MBq), and had a 45% retreatment rate. The dose was calculated taking into consideration the 24-hour I-131 thyroid uptake, calculated thyroid weight, the effective half-life (days) of I-131, and the dose of I-131. The patients who required multiple doses presented with more severe hyperthyroidism, and the majority of them were of Negroid origin. They also noted that younger patients required a longer period of time to become hypothyroid.

Having administered average doses of RAI of 299 MBq to male patients and 301 MBq to the females, Allahabadia et al¹² concluded that younger patients and those of male gender were more likely to have a poor response to RAI. Forty-seven percent of their male patients were cured with a single dose in contrast to 74% of the women; administration of a second dose of RAI to the men achieved a slightly higher cure rate of 53%.

A retreatment rate of 10% was found in 556 patients (91 males and 465 females) with GD and toxic nodular goitre studied by Berg et al.¹¹⁴ These patients had been treated with a single dose calculated to deliver 100-120 Gy to the thyroid gland. The mean activities administered to their patients were 386 ± 136 MBq (GD) and 461 ± 115 MBq (TNG). The study by El Refaei et al¹⁷ showed a retreatment rate of 19%, after administering doses of 370 MBq to their patients. Our study had a relatively lower retreatment rate of 15.9% despite the fact that patients were given lower first doses (an mean of 330.1 ± 72.9 MBq).

Conclusion

Our study was conducted to confirm or refute the assumption that RAI therapy in our male hyperthyroid patients is less successful than in their female counterparts. The similar outcomes experienced by both male and female patients in this study, despite higher doses in the former, may lend more weight to the belief that hyperthyroidism in male patients is more difficult to treat than in female patients, and that male patients will benefit from higher doses of RAI than their female counterparts. This is supported by the finding that men who received a relatively low dose of RAI (<250 MBq) had significantly higher free T4 and T3 levels 3 months after the administration of the RAI.

Limitations

The main limitations in the study were the loss of patients to follow-up and missing records. Our conclusions are therefore only based on the 3 months follow-up findings, which is most likely not a true reflection of the final outcome of the patients.

References

- ¹ Robbins SL, Cotran RS, Kumar V, Collins T. Pathologic basis of disease. 6th ed. 1999; Philadelphia: WB Saunders. p.1130-1141.
- ² Ziessman HA, O'Malley JP, Thrall JH. Nuclear medicine: The requisites in radiology. 3rd ed. 2006; Philadelphia: Elsevier Mosby.
- ³ Van der Molen AJ, Thomsen HS, Morcos SK. Effect of iodinated contrast media on thyroid function in adults. *Eur Radiol* 2004; 14:902-907.
- ⁴ Tuttle RM, Becker DV, Hurley JR. Radioiodine treatment of thyroid disease. In: Sandler MP, Coleman RE, Patton JA, Wackers FJT, Gottschalk A, editors. 4th ed. 2003; Philadelphia: Lippincott Williams and Wilkins.
- ⁵ Jameson JL, Weetman AP. Disorders of the thyroid gland. In: Braunwald E, Fauci AS, Kasper DL, James JL, editors. *Harrison's principles of internal medicine*. 15th ed. 2001; New York: McGraw Professional Publishing.
- ⁶ Franklyn JA. Management of hyperthyroidism. *N Engl J Med* 1994; 330:1731-1738.
- ⁷ Tunbridge WMG, Evered DC, Hall R, Appleton D, Brewis M, Clark F, et al. The spectrum of thyroid disease in a community: the Wickham survey. *Clin Endocrinol* 1977;7:481-493.
- ⁸ Howlett TA. Endocrine disease. In: Kumar P, Clark M, editors. *Clinical medicine*. 6th ed. 2005; Edinburgh: Elsevier Saunders.
- ⁹ Sarkar SD. Benign thyroid disease: what is the role of nuclear medicine? *Semin Nucl Med* 2005; 36:185-193.
- ¹⁰ Glinoe D, Hesch D, Lagasse R, Laurberg P. The management of hyperthyroidism due to Graves' disease in Europe in 1986. Results of an international survey. *Acta Endocrinol Suppl* 1987; 115:1-23.
- ¹¹ Wartofsky L, Glinoe D, Solomon B, Lagasse R. Differences and similarities in the diagnosis and treatment of Graves' disease in Europe, Japan and the United States. *Thyroid* 1991; 1:129-135.
- ¹² Allahabadia A, Daykin J, Holder RL, Sheppard MC, Gough SCL, Franklyn JA. Age and gender predict the outcome of treatment for Graves' hyperthyroidism. *J Clin Endocrinol Metab*. 2000; 85:1038-1042.
- ¹³ Allahabadia A, Daykin J, Sheppard MC, Gough SCL, Franklyn JA. Radioiodine treatment of hyperthyroidism – prognostic factors for outcome. *J Clin Endocrinol Metab* 2001; 86:3611-3617.
- ¹⁴ Velkeniers B, Cytyn R, Vanhaelst L, Jonckheer MH. Treatment of hyperthyroidism with radioiodine: adjunctive therapy with antithyroid drugs reconsidered. *Lancet* 1988;1:1127-1129.
- ¹⁵ Fisher JN. Management of thyrotoxicosis. *South Med J* 2002; 95:493-505.

-
- ¹⁶ Reynolds LR, Kotchen TA. Antithyroid drugs and radioactive iodine- fifteen years' experience with Graves' disease. *Arch Intern Med* 1979; 139:651-653.
- ¹⁷ El Refaei SM, Shawkat W. Long-term carbimazole intake does not affect success rate of radioactive ¹³¹iodine treatment of Graves' disease. *Nucl Med Comm* 2008; 29:642-648.
- ¹⁸ Blahd WH, Hays MT. Graves' disease in the male. *Arch Intern Med* 1972; 129:33-40.
- ¹⁹ Ganong WF. Review of medical physiology. 22nd ed. 2005; New York: Lange.
- ²⁰ Greenspan FS, Rapoport B. Thyroid gland. In: Greenspan FS, Forsham PH, editors. *Basic and clinical endocrinology*, 2nd ed. 1986; Connecticut:Appleton-Century-Crofts. p.143-170.
- ²¹ Goldsmith SJ: Endocrine system. In Bernier DR, Christian PE, Langan JK, editors: *Nuclear medicine technology and techniques*, 3rd ed. 1994; St Louis: Mosby.
- ²² Davies AG. Thyroid physiology. *BMJ* 1972; 2:206-209.
- ²³ Dunn JT, Dunn AD. Thyroid physiology. In: Besser GM, Thorner MO, editors. *Comprehensive clinical endocrinology*, 3rd ed. 2002; Edinburgh: Mosby. p. 131-138.
- ²⁴ Junqueira LC, Carneiro J, Kelley RO. *Basic histology*. 7th ed. 1992; London: Prentice-Hall International Inc.
- ²⁵ Larsen PR, Davies TF, Schlumberger MJ, Hay ID. Thyroid physiology and diagnostic evaluation of patients with thyroid disorders. In: Larsen PR, Kronenberg HM, Melmed S, Polonsky KS, editors. *Williams' textbook of endocrinology*, 10th ed. 2003; Pennsylvania, Saunders.
- ²⁶ Dadachova E, Carrasco N. The Na⁺/I⁻ symporter (NIS): imaging and therapeutic applications. *Semin Nucl Med* 2004; 34:23-31.
- ²⁷ Wheater PR, Burkitt GH, editors. *Functional histology: a text and colour atlas*. 2nd ed. 1987; Edinburgh: Churchill Livingstone.
- ²⁸ Young B, Heath JW, editors. *Wheater's functional histology: a text and colour atlas*. 4th ed. 2000; Edinburgh: Churchill Livingstone. p.315-317.
- ²⁹ Dunn JT, Dunn AD. Update on intrathyroidal iodine metabolism. *Thyroid* 2001; 11:407-414.
- ³⁰ Qari FA. Trends in the diagnostic and therapeutic approach to Graves' disease at a university hospital. c2007. Available from:
www.bhj.org/journal/april2005/htm/original_trends_122.htm
Accessed 7th March 2007
- ³¹ Davies TF. Graves' disease. In: Braverman LE, Utiger RD, editors. *Werner and Ingbar's The Thyroid*. 7th ed. 1996; Philadelphia: Lippincott.
- ³² Bech K. *Yersinia enterocolitica* and thyroid autoimmunity [Abstract]. *Autoimmunity* 1990; 7:291-294.

-
- ³³ Wolf MW, Misaki T, Bech K, Tvede M, Silva JE, Ingbar SH. Immunoglobulins of patients recovering from *Yersinia enterocolitica* infections exhibit Graves' disease-like activity in human thyroid membranes. *Thyroid* 1991; 1:315-320.
- ³⁴ Tomer Y, Davies TF. Infections and autoimmune endocrine disease [Abstract]. *Baillieres Clin Endocrinol Metab* 1995; 9:47-70.
- ³⁵ Becker DV, Charkes ND, Hurley JR, McDougall IR, Price DC, et al. Procedure guideline for thyroid scintigraphy. Society of Nuclear Medicine. Version 2.0, approved February 7, 1999. Available from:
http://interactive.snm.org/docs/pg_ch05_0403.pdf
Last accessed 1st November 2008
- ³⁶ Procedure guideline for thyroid imaging. British Nuclear Medicine Society. Approved January 2007, updated September 2008. Available from:
http://www.bnmsonline.co.uk/index.php?option=com_content&task=view&id=43&Itemid=151
Last accessed 1st November 2008
- ³⁷ Peters AM, editor. *Nuclear medicine in radiological diagnosis*. 2003; London: Martin Dunitz.
- ³⁸ Saha GB. *Fundamentals of nuclear pharmacy*. 5th ed. 2004; New York: Springer.
- ³⁹ Atkins HL. Technetium-99m pertechnetate uptake and scanning in the evaluation of thyroid function. *Semin Nucl Med* 1971; 1:345-355.
- ⁴⁰ McGill PE, Harden RM, Robertson IWK, Shimmins J. A comparison between the uptake of Technetium-99m and Iodine-131 by the thyroid gland. *J Endocr* 1971; 49:531-536.
- ⁴¹ Ramos CD, Wittmann DEZ, Etchebere ECS, Tambacsia MA, Silva CAM, Camargo EE. Thyroid uptake and scintigraphy using Tc-99m pertechnetate: standardization in normal individuals. *Sao Paulo Med J/Rev Paul Med* 2002; 120:45-48.
- ⁴² Hooper PL, Caplan RH. Thyroid uptake of radioactive iodine in hyperthyroidism. *JAMA* 1977; 238:411-413.
- ⁴³ Meier DA, Kaplan MM. Radioiodine uptake and thyroid scintiscanning. *Endocrinol Metab Clin North Am* 2001; 30:291-313.
- ⁴⁴ Berg GEB, Michanek AMK, Holmberg ECV, Fink M. Iodine-131 treatment of hyperthyroidism: significance of effective half-life measurements. *J Nucl Med* 1996; 37:228-232.
- ⁴⁵ Hamburger JJ. Application of the radioiodine uptake to the clinical evaluation of thyroid disease. *Semin Nucl Med* 1971; 1:287-300.
- ⁴⁶ Aktay R, Rezai K, Seabold JE, Bar RS, Kirchner PT. Four-to twenty-four hour uptake ratio: an index of rapid iodine-131 turnover in hyperthyroidism. *J Nucl Med* 1996; 37:1815-1819.

-
- ⁴⁷ Hennessy JV, Berg LA, Ibrahim MA, Markert RJ. Evaluation of early (5 to 6 hours) iodine-123 uptake for diagnosis and treatment planning in Graves' disease. *Arch Intern Med* 1995; 155:621-624.
- ⁴⁸ Becker DV, Charkes ND, McDougall Ross, Price DC. Procedure guideline for thyroid uptake measurement. Society for Nuclear Medicine, version 3.0. Approved September 5, 2006. Available from:
<http://interactive.snm.org/docs/Thyroid%20Uptake%20Measure%20v3%200.pdf>
Last accessed 1st November 2008
- ⁴⁹ Van't Hoff W, Pover GG, Eiser NM. Technetium-99m in the diagnosis of thyrotoxicosis. *BMJ* 1972; 4:203-206.
- ⁵⁰ Davies TF, Ando T, Lin R, Tomer Y, Latif R. Thyrotropin receptor-associated diseases: from adenomata to Graves' disease. *J Clin Invest* 2005; 115:1972-1983.
- ⁵¹ Orgiazzi J. Anti-TSH receptor antibodies in clinical practice. *Endocrinol Metab Clin North Am* 2000; 29:339-355.
- ⁵² Ginsberg J. Diagnosis and management of Graves' disease. *CMAJ* 2003; 168:575-585.
- ⁵³ Gharib H, Papini E, Valvari R. American Association of Clinical Endocrinologists and Asociazione Medici Endocrinologi Medical Guidelines for clinical practice for the diagnosis and management of thyroid nodules. *Endocr Pract* 2006; 12:63-102.
- ⁵⁴ Cooper DS, Doherty GM, Haugen BR, et al. Management guidelines for patients with thyroid nodules and differentiated thyroid cancer. The American Thyroid Association Guidelines Taskforce. *Thyroid* 2006; 16:1-33.
- ⁵⁵ Oertel YC. Fine needle aspiration of the thyroid: technique and terminology. *Endocrinol Metab Clin N Am* 2007; 36:737-751.
- ⁵⁶ Hegedüs L, Bonnema SJ, Bennedbæk FN. Management of simple nodular goitre: current status and future perspectives. *Endocrine Reviews* 2003; 24:102-132.
- ⁵⁷ Christensen CR, Glowniak JV, Brown PH, Morton KA. The effect of gadolinium contrast media on radioiodine uptake by the thyroid gland. *J Nucl Med Technol* 2000; 28:41-44.
- ⁵⁸ Cooper DS. Drug therapy: antithyroid drugs. *N Engl J Med* 2005; 352:905-917.
- ⁵⁹ AACE Thyroid Task Force. American Association of Clinical Endocrinologists medical guidelines for clinical practice for the evaluation and treatment of hyperthyroidism and hypothyroidism. *Endocr Pract* 2002; 8:457-469.
- ⁶⁰ Singer PA, Cooper DS, Levy EG, Ladenson PW, et al. American Thyroid Association treatment guidelines for patients with hyperthyroidism and hypothyroidism. *JAMA* 1995; 273:808-812.

-
- ⁶¹ Esselstyn CB, Crile G. Indications for surgical therapy in thyroid disease. *Semin Nucl Med* 1971; 1:474-480.
- ⁶² British National Formulary. March 2007; London: BMJ publishing group.
- ⁶³ Patel NN, Abraham P, Buscombe J, Vanderpump MPJ. The cost effectiveness of treatment modalities for thyrotoxicosis in a U.K. centre. *Thyroid* 2006; 16:593-598.
- ⁶⁴ Pradeep PV, Agarwal A, Baxi M, Agarwal G, Gupta SK, Mishra SK. Safety and efficacy of surgical management of hyperthyroidism: a 15-year experience from a tertiary care centre in a developing country. *World J Surg* 2007; 31:306-312.
- ⁶⁵ Beierwaltes WH. The treatment of hyperthyroidism with Iodine-131. *Semin Nucl Med* 1978; 8:95-103.
- ⁶⁶ Mettler FA, Guiberteau, editors. *Essentials of nuclear medicine imaging*. 5th ed. 2006; Philadelphia: Saunders.
- ⁶⁷ Gold A. Radioactive iodine in the treatment of thyroid diseases. *CMAJ* 1951; 64:536-539.
- ⁶⁸ Silberstein EB, Alavi A, Balon HR, Becker DV, Brill DR, Clarke SEM, et al. Procedure guideline for treatment of thyroid disease with iodine-131 (sodium iodide). Version 2.0. Available from: <http://interactive.snm.org/docs/Therapy%20of%20Thyroid%20Disease%20with%20Iodine-131%20v2.0.pdf>
- Accessed 1st November 2008
- ⁶⁹ Wagner HN, Szabo Z, Buchanan JW, editors. *Principles of nuclear medicine*. 2nd ed. 1995; Philadelphia: Saunders.
- ⁷⁰ Bartalena L, Pinchera A, Marcocci C. Management of Graves' ophthalmopathy: reality and perspectives. *Endocr Rev* 2000; 21:168-199.
- ⁷¹ Jarlov AE, Hegedus L, Kristensen LO, Nygaard B, Hansen JM. Is calculation of the dose in radioiodine therapy of hyperthyroidism worthwhile? *Clin Endocrinol (Oxf)* 1995; 43:325-329.
- ⁷² Van Isselt, De Klerk JM, Koppeschaar HPF, Van Rijk PP. Iodine-131 uptake and turnover rate vary over short intervals in Graves' disease. *Nucl Med Comm* 2000; 21:609-616.
- ⁷³ Sterling K. Radiothyroxine turnover studies in thyroid disease after therapy. *J Clin Invest* 1958; 37:1348-1356.
- ⁷⁴ Barandes M, Hurley JR, Becker DV. Implications of rapid intrathyroidal turnover for I-131 therapy: the small-pool syndrome [Abstract]. *J Nucl Med* 1973; 14:379.
- ⁷⁵ Zanzonico PB, Becker DV, Hurley JR. Enhancement of radioiodine treatment of small-pool hyperthyroidism with antithyroid drugs: kinetics and dosimetry. *J Nucl Med* 2004; 45:2102-2108.
- ⁷⁶ Dworkin HJ, Meier DA, Kaplan M. Advances in the management of patients with thyroid disease. *Semin Nucl Med* 1995; 3:205-220.

-
- ⁷⁷ Sridama V, McCormick M, Kaplan EL, Fauchet R, De Groot LJ. Long-term follow-up study of compensated low-dose I-131 therapy for Graves' disease. *N Engl J Med* 1984; 311:426-432.
- ⁷⁸ Willemsen UF, Kensewitch P, Kreisig T, Pickardt CR, Kirch CM. Functional results of radioiodine therapy with a 300-Gy absorbed dose in Graves' disease. *Eur J Nucl Med* 1993; 20:1051-1055.
- ⁷⁹ Nordyke RA, Gilbert FI. Optimal I-131 dose for eliminating hyperthyroidism in Graves' disease. *J Nucl Med* 1991; 32:411-416.
- ⁸⁰ Farrar JJ, Toft AD. Iodine-131 treatment of hyperthyroidism: current issues. *Clin Endocrinol* 1991; 35:207-212.
- ⁸¹ Tarantini A, Ciuoli C, Di Cairano G, Guarino E, Mazzucato P, Montanaro A, et al. Effectiveness of radioiodine (I-131) as definitive therapy in patients with autoimmune and non-autoimmune hyperthyroidism. *J Endocrinol Invest* 2006; 29:594-598.
- ⁸² Nygaard B, Hegedus L, Uriksen P, Nielsen KG, Hansen JM. Radioiodine therapy for multinodular toxic goitre. *Arch Intern Med* 1999; 159:1364-1368.
- ⁸³ Holm LE, Lundell G, Dahlqvist I, Israelsson A. Cure rate after ¹³¹I therapy for hyperthyroidism. *Acta Radiol (Oncol)* 1981; 20:161-166.
- ⁸⁴ Charkes ND. Graves' disease with functioning nodules (Marine-Lenhart syndrome). *J Nucl Med* 1972; 13:885-892.
- ⁸⁵ Manji N, Carr-Smith JD, Boelaert K, Allahabadia A, Armitage M, Chatterjee VK, Lazarus JH, Pearce SHS, Vaidya B, Gough SC, Franklyn JA. Influences of age, gender, smoking and family history on autoimmune thyroid disease phenotype. *J Clin Endocrinol Metab* First published ahead of print September 12, 2006 as doi:10.1210/jc.2006-1402
- ⁸⁶ Ceccarelli C, Bencivelli W, Vitti P, Grasso L, Pinchera A. Outcome of radioiodine-131 therapy in hyperfunctioning thyroid nodules: a 20 years' retrospective study. *Clin Endocrinol* 2005; 62:331-335.
- ⁸⁷ Kendall-Taylor P, Keir MJ, Ross WM. Ablative radioiodine therapy for hyperthyroidism: long-term follow-up study. *BMJ* 1984; 289:361-363.
- ⁸⁸ Franklyn JA, Daykin J, Drolc Z, Farmer M, Sheppard MC. Long term follow-up of treatment of thyrotoxicosis by three different methods. *Clin Endocrinol (Oxf)* 1991; 34:71-76.
- ⁸⁹ Pearce EN. Diagnosis and management of thyrotoxicosis. *BMJ* 2006; 332:1369-1373.
- ⁹⁰ Bartalena L, Marcocci C, Bogazzi F, Panicucci M, Lepri A, Pinchera A. Use of corticosteroids to prevent progression of Graves' ophthalmopathy after radioiodine therapy for hyperthyroidism. *N Engl J Med* 1989; 321:1349-1352.

-
- ⁹¹ Sridama V, De Groot L. Treatment of Graves' disease and the course of ophthalmopathy. *Am J Med* 1989; 87:70-73.
- ⁹² Talledst T, Lundell G, Topping O, Wallin G, Ljunggren JG, Blomgren H, et al. Occurrence of ophthalmopathy after treatment for Grave's hyperthyroidism. The Thyroid Study Group. *N Engl J Med* 1992; 326:1773-1778.
- ⁹³ Graham GD, Burham KD. Radioiodine treatment of Graves' disease. An assessment of its potential risks. *Ann Intern Med* 1986; 105:900-905.
- ⁹⁴ Pochin EE. Leukaemia following radioiodine treatment of thyrotoxicosis. *BMJ* 1960; 2:1545-1550.
- ⁹⁵ Saenger EL, Thomas GE, Thompkins EA. Incidence of leukaemia following treatment of hyperthyroidism: cooperative thyrotoxicosis follow-up study. *JAMA* 1968; 205:855-862.
- ⁹⁶ Dobyns BM, Shelline GE, Workman JB. Malignant and benign neoplasms of the thyroid in patients treated for hyperthyroidism: a report of the cooperative thyrotoxicosis therapy follow-up study. *J Clin Endocrinol Metab* 1974; 38:976-978.
- ⁹⁷ Freitas JE, Swanson DP, Gross MD, Sisson JC. Iodine I-131: optimal therapy for hyperthyroidism in children and adolescents? *J Nucl Med* 1979; 20:847-850.
- ⁹⁸ Hamburger JI. Management of hyperthyroidism in children and adolescents. *J Clin Endocrinol Metab* 1985; 60:1019-1024.
- ⁹⁹ Hayek A, Chapman EM, Crawford JD. Long term results of treatment of thyrotoxicosis in children and adolescents with radioactive iodine. *N Engl J Med* 1970; 283:949-953.
- ¹⁰⁰ Safa AM, Schumacher OP, Rodriguez-Antunea A. Long term follow-up results in children and adolescents treated with radioactive iodine (I-131) for hyperthyroidism. *N Engl J Med* 1975; 292:167-170.
- ¹⁰¹ Metso S, Jaatinen P, Huhtala H, Luukaala T, Oksala H, Salmi J. Long-term follow-up study of radioiodine treatment of hyperthyroidism. *Clin Endocrinol (Oxford)* 2004; 61:641-648.
- ¹⁰² Mackin JF, Canary JJ, Pittman CS. Thyroid storm and its management. *N Engl J Med* 1974; 291:1396-1398.
- ¹⁰³ Dworkin HJ. Treatment of diffuse toxic goitre with ¹³¹I. *Sem Nucl Med* 1971; 1:399-410.
- ¹⁰⁴ Gharib H, Tuttle RM, Baskin HJ, Fish LH, Singer PA, McDermott MT. Consensus statement: subclinical thyroid dysfunction: a joint statement on management from the American Association of Clinical Endocrinologists, the American Thyroid Association, and the Endocrine Society. *J Clin Endocrinol Metab*. 2005; 581-5.
- ¹⁰⁵ Ross DS. Subclinical hypothyroidism. In: Braverman E, Utiger RD, editors. *Werner and Ingbar's The thyroid; a fundamental and clinical text*. 7th ed. 1997; Philadelphia: Lippincott-Raven.

-
- ¹⁰⁶ Beckett GJ, Toft AD. First-line thyroid function tests - TSH alone is not enough. [Commentary] *Clin Endocrinol* 2003; 58:20-21.
- ¹⁰⁷ Efron B, Tibshirani R. *An introduction to the bootstrap*. 1993; London: Chapman and Hall.
- ¹⁰⁸ Iagaru A, McDougall R. Treatment of thyrotoxicosis. *J Nucl Med* 2007; 48:379-387
- ¹⁰⁹ Leslie WD, Ward L, Salamon EA, Ludwig S, Rowe RC, Cowden EA. A randomized comparison of radioiodine doses in Graves' hyperthyroidism. *J Clin Endocrinol Metab* 2003; 88:978-983.
- ¹¹⁰ Yamashita Y, Yamane K, Tamura T, Okubo M, Kohno N. Onset age is associated with outcome of radioiodine therapy in Graves' disease. *Endocr J* 2004; 51:127-132.
- ¹¹¹ McGregor AM, Smith BR, Hall R, Petersen MM, Miller M, Dewar PJ. Prediction of relapse in hyperthyroid Graves' disease. *The Lancet* 1980; 1:1101-1103.
- ¹¹² Prakash R. Prediction of remission in Graves' disease treated with long-term carbimazole therapy: evaluation of technetium-99m thyroid uptake and TSH concentrations as prognostic factors. *Eur J Nucl Med* 1996; 23:118-122.
- ¹¹³ Zantut-Wittman DE, Ramos CD, Santos AO, Lima MAM, Panzan AD, Facuri FO, et al. High pre-therapy [^{99m}] pertechnetate thyroid uptake, thyroid size and thyrostatic drugs: predictive factors of failure in [¹³¹] iodide therapy in Graves' disease. *Nucl Med Comm* 2005; 26:957-963.
- ¹¹⁴ Berg G, Michanek A, Holmberg E, Nyström E. Clinical outcome of radioiodine treatment of hyperthyroidism: a follow-up study. *J Internal Med* 1996; 239:165-171.